Managing Immune Checkpoint-Blocking Antibody Side Effects

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OVERVIEW

Immune checkpoint-blocking antibodies that enhance the immune system’s ability to fight cancer are becoming important components of treatment for patients with a variety of malignancies. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) was the first immune checkpoint to be clinically targeted, and ipilimumab, an inhibitor of CTLA-4, was approved by the U.S. Food and Drug Administration (FDA) for patients with advanced melanoma. The programmed cell death-1 (PD-1) receptor and one of its ligands, PD-L1, more recently have shown great promise as therapeutic targets in a variety of malignancies. Nivolumab and pembrolizumab recently have been FDA-approved for patients with melanoma and additional approvals within this therapeutic class are expected. The use of anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is associated with side effects known as immune-related adverse events (irAEs). Immune-related adverse events affect the dermatologic, gastrointestinal, hepatic, endocrine, and other organ systems. Temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or other agents can be effective treatment. This article describes the side-effect profile of the checkpoint-blocking antibodies that target CTLA-4 and PD-1/PD-L1 and provides suggestions on how to manage specific irAEs.

The immune system plays an important role in controlling and eradicating cancer. Recently, strategies that enhance T-cell function by blocking negative regulatory components on T cells, which are called checkpoints, have led to remarkable success for patients with many different malignancies. CTLA-4 was the first T-cell checkpoint to be clinically targeted. Ipilimumab, an anti-CTLA-4 antibody, was approved by the FDA for patients with advanced melanoma based on an overall survival benefit.1,2 A second immunologic checkpoint, known as PD-1, and its predominant ligand, PD-L1, also is demonstrating incredible promise as a therapeutic target. Nivolumab and pembrolizumab (anti-PD–1 blocking antibodies) have been FDA-approved for patients with advanced melanoma.3,4 Nivolumab and pembrolizumab, and additional antibodies that target the PD-1 axis, are also effective in additional cancers such as non-small cell lung cancer, renal cell cancer, bladder cancer, and Hodgkin lymphoma.5-9

Although these antibodies can be associated with substantial benefits, by increasing immune system function, immune-checkpoint blockade can lead to inflammatory side effects called immune-related adverse events (irAEs). Immune-related adverse events can affect any organ system, but they typically involve the skin, gastrointestinal, hepatic, and endocrine systems. Temporary use of immunosuppressive medications can suppress these side effects without eliminating the possibility of a favorable antitumor response. This review focuses on irAEs associated with antibodies that block the immunologic checkpoints, CTLA-4 and PD-1, including antibodies that block the ligand of PD-1/PD-L1. These agents have been studied most extensively in patients with melanoma, and experience and recommendations are based primarily on data obtained from studies involving patients with melanoma. Nevertheless, the principles of irAE recognition and management are relevant across the oncologic spectrum and will become increasingly important as the use of these antibodies expands.

SPECIFIC TYPES OF IMMUNE-RELATED ADVERSE EVENTS AND MANAGEMENT

Rash and Mucosal Irritation

The most common and typically earliest onset (Fig. 1) irAE associated with checkpoint inhibitors is dermatologic toxicity.10 Nearly 50% of patients treated with ipilimumab will experience rash and/or pruritus. Rashes associated with checkpoint blockade often appear as faintly erythematous, reticular, and maculopapular. Typically, the trunk and extremities are involved.11 In one case, neutrophilic infiltration, diagnostic of Sweet’s Syndrome, was reported.12 Vitiligo also can be seen, although it typically does not appear until months after the initiation of checkpoint blockade. Topical corticosteroid creams can be used to treat rash induced by checkpoint blockade. Oral antipruritics (hy-
Droxylazine HCl or diphenhydramine HCl can help if pruritus is problematic. Severe rashes (grade 3 and above) should be managed with oral corticosteroids. Consideration of permanent discontinuation of checkpoint blockade because of reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis rarely have been reported. Such reactions require hospitalization for intravenous corticosteroids, dermatologic evaluation, and fluid/electrolyte management.

Antibodies that block PD-1/PD-L1 also can result in dermatologic/mucosal toxicity. Anecdotal cases of patients with oral mucositis and/or dry mouth symptoms have been described with PD-1/PD-L1 treatment. In a large phase I trial of nivolumab, 6.5% of patients had symptoms of dry mouth; one patient had symptoms of grade 3 dry mouth. Oral corticosteroids rinses or lidocaine can treat this symptom effectively. Since many patients with this complaint may be receiving concomitant immunosuppression to treat another irAE, oral candidiasis remains in the differential diagnosis.

Diarrhea is common in patients undergoing treatment with checkpoint-blocking antibodies. However, there is a much higher incidence of diarrhea in patients receiving CTLA-4 blocking antibodies compared to those targeting PD-1/PD-L1. When considering the occurrence of this irAE, distinguishing diarrhea (increase in frequency of stool) from colitis (abdominal pain, radiographic or endoscopic findings of colonic inflammation) is important. For patients with melanoma undergoing CTLA-4 blockade with ipilimumab, approximately 30% had diarrhea of any grade and less than 10% had severe (grade 3/4) diarrhea. Rates of grade 3/4 colitis have been found to affect only approximately 5% of treated patients. Patients should be informed that diarrhea/colitis does not typically begin with initiation of checkpoint blockade; instead, it usually begins approximately 6 weeks into treatment (Fig. 1).

Diarrhea/colitis with CTLA-4 blockade is more common than with PD-1/PD-L1 blockade. The rate of grade 3/4 diarrhea in patients treated with PD-1/PD-L1 agents is very low (1% to 2%). Although the precise safety profile is still under evaluation, patients who had significant diarrhea/colitis during CTLA-4 blockade have been treated with PD-1 therapy without diarrhea/colitis recurrence. Nonetheless, ongoing trials and clinical experience are necessary to more fully understand the safety of PD-1/PD-L1 blockade in this setting.

When a patient presents with mild diarrhea, clinicians should consider other etiologies that may be responsible, such as *Clostridium difficile* infection or other bacterial/viral pathogens. Patients should be counseled on the importance of maintaining oral hydration. Some clinicians find that the American Dietary Association’s colitis diet and antimitoty agents (oral diphenoxylate HCl and atropine sulfate 4 times a day) can be helpful. If symptoms persist for more than 3 days, or increase, and/or no infectious causes are readily identified, the use of oral or intravenous corticosteroids are required.

In severe cases or situations in which symptoms do not improve with oral corticosteroids, hospitalization for intravenous corticosteroids, hydration, and electrolyte management is required. A colonoscopy is not necessarily indicated unless the diagnosis is unclear. If intravenous corticosteroids (up to 2 mg/kg methylprednisolone twice a day) do not lead to symptom resolution, infliximab (Remicade; Janssen Biotech, Horsham, PA) at a dose of 5 mg/kg, once every 2 weeks can be helpful. The use of infliximab in this setting is based on its use in patients with inflammatory bowel diseases. In very rare cases, colitis can result in bowel perforation that can potentially require colostomy.

Unfortunately, there are no proven treatments to prevent the occurrence of diarrhea. In one study, prophylactic use of the matrix-release corticosteroid budesonide was not found to be helpful. Nevertheless, some clinicians find budesonide to be helpful in early treatment for mild noninfectious
diarrhea symptoms that persist but do not escalate after 2 to 3 days of dietary modification and antimitotility agents.

**HEPATOTOXICITY**

Hepatitis, as determined by elevations in aspartate aminotransferase (AST), aminotransferase (ALT) and less commonly, total bilirubin, occasionally is seen in patients treated with checkpoint blockade. Although most episodes present only as asymptomatic laboratory abnormalities, some patients have an associated fever. Rates of AST and ALT elevations with CTLA-4 blockade vary among clinical trials, but they typically have been reported in less than 10% of patients. In large trials of PD-1–blocking antibodies, the rates of hepatitis were similarly low (below 5%) and grade 3/4 toxicity was even rarer. Among patients who develop hepatitis, the most common onset is 8 to 12 weeks after initiation of treatment, although early or delayed events also may be seen. Radiographic findings are not typical. In severe cases, however, findings on CT scans may include mild hepatomegaly, periportal edema, or periportal lymphadenopathy. Liver biopsies have described pathologic changes that include severe panlobular hepatitis with prominent perivenular infiltrates with endothelialitis or a primary biliary pattern with mild portal mononuclear infiltrate around bile ductules. Hepatic function (transaminases and bilirubin) should be monitored before each dose of ipilimumab. If AST and ALT increase, viral and other drug-induced causes of hepatitis should be excluded. As with treating other irAEs, if no other cause is obvious, prompt treatment with corticosteroids is necessary. In rare cases, elevations in AST and ALT are steroid-refractory and 500 mg every 12 hours of cyclophosphamide (CellCept; Genentech, South San Francisco, CA) may be helpful. The use of antithymocyte globulin therapy also was described in a case report. Unlike for patients with diarrhea/colitis, infliximab should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity. Hepatitis may persist for quite some time and require prolonged or repeated corticosteroid tapers (minimum of 3 weeks suggested) and/or additional immunosuppression.

**ENDOCRINOPATHY**

Immune-related adverse events that affect the pituitary, adrenal, and thyroid glands often present with nonspecific symptoms such as nausea, headache, and fatigue. The incidence of endocrinopathy has been difficult to precisely determine because of the variable methods of assessment, diagnosis, and monitoring in each clinical trial. Nonetheless, hypophysitis (pituitary inflammation) and hypothyroidism are the most common endocrinopathies and are typically believed to occur in up to 10% of patients treated with CTLA-4 blockade. When hypophysitis is suspected, all or some of the hormones released by the pituitary may be reduced (adrenocorticotropic hormone [ACTH], thyroid stimulating hormone [TSH], follicle stimulating hormone, luteinizing hormone, growth hormone, prolactin). Typically, hypophysitis is diagnosed by clinical symptoms of fatigue and headache, radiographic findings (enhancement and enlargement of the pituitary), and biochemic evidence of pituitary dysfunction (low ACTH and TSH). Biochemical tests associated with hypophysitis are distinct from primary adrenal insufficiency (low cortisol or inappropriate cortisol stimulation test; high ACTH) and primary hypothyroidism (low free T4; high TSH).

When hypophysitis is suspected, some clinicians have anecdotally described that a course of high-dose corticosteroids (1 mg/kg of prednisone daily) given during the acute phase can reverse the inflammatory process and prevent the need for longer-term hormone replacement. In almost all patients, however, longer-term supplementation of affected hormones is necessary because of secondary hypothyroidism (treated with levothyroxine) or secondary hypoadrenalism (treated with replacement doses of hydrocortisone, typically 20 mg each morning and 10 mg each evening). Some authors have described that patients can be successfully weaned from replacement corticosteroids over time, but this is likely the exception. The immunologic mechanisms of hypophysitis are unknown, but they may be related to the development of humoral (antibody) immunity against the pituitary gland and subsequent complement activation.

Since routine monitoring of thyroid function tests (TSH) is required before each dose of ipilimumab, patients often are diagnosed with thyroid abnormalities (hyperthyroidism and hypothyroidism) as a result of checkpoint blockade. Hypothyroidism is believed to occur far more commonly than hyperthyroidism. When patients are evaluated for fatigue that is possibly a result of endocrinopathy, it is important to distinguish primary hypothyroidism (low free T4 and high TSH) from hypophysitis, which can result in secondary hypothyroidism (low free T4 and low TSH). Management of hypothyroidism involves replacement with thyroid hormone (levothyroxine).

The most emergent endocrinopathy is an adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances such as hyperkalemia and hyponatremia. When this occurs, intravenous corticosteroids and immediate hospitalization is required. Consultation with an endocrinologist, aggressive hydration, and evaluation for sepsis is critical.

The frequency of endocrinopathy in patients treated with PD-1/PD-L1 agents is not known yet, but it may differ from those seen with CTLA-4 blockade. Hypophysitis rarely has been described in published trials of PD-1 blockade for patients with advanced melanoma. Thyroid disorders have been described in less than 10% of patients. Some cases, however, can be severe. Treatment of endocrinopathy with PD-1/PD-L1 agents is approached in a way similar to treating patients undergoing CTLA-4 blockade.
LESS FREQUENTLY INVOLVED ORGANS

Lung
Several pulmonary inflammatory conditions have been seen in patients treated with ipilimumab, including sarcoidosis and organizing inflammatory pneumonia. Pneumonitis also has been described in patients treated with PD-1 blocking agents (<10%) but with occasional fatal consequence in early trials. In any patient presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, or shortness of breath, pneumonitis should be considered and evaluated with imaging. In moderate to severe cases, a bronchoscopy should be performed to exclude infectious etiologies before starting immunosuppression. In severe cases, treatment should consist of high doses of corticosteroids such as 2 mg/kg of intravenous methylprednisolone. Additional immunosuppression with infliximab, mycophenolate mofetil, or cyclophosphamide is reasonable.

Eye
Inflammation of components of the eye has been described with CTLA-4 blockade. These include episcleritis, conjunctivitis, and uveitis. Typically, the incidence is believed to be less than 1%, and symptoms can include photophobia, pain, dryness of the eyes, and blurry vision. Consultation with an ophthalmologist is recommended, and treatment with topical intraocular corticosteroids such as 1% prednisolone acetate suspension may be helpful. Oral corticosteroids can be used for more severe (grade 3/4 or refractory) cases. The incidence of ophthalmologic toxicity in patients treated with PD-1/PD-L1 blockade is less-well described, but it is likely an infrequent side effect.

Kidney
Several case reports have described patients treated with ipilimumab who have developed renal insufficiency believed to be related to treatment. Histopathologic analyses of kidney biopsies have described several different pathologic processes, including acute granulomatous interstitial nephritis and lupus membranous nephropathy. Treatment with oral or intravenous corticosteroids in these cases has been associated with improvement in renal function. Renal insufficiency with PD-1 agents and the combination of CTLA-4 and PD-1 blockade similarly has been reported in several patients with anecdotal findings of interstitial nephritis and response to corticosteroids.

Pancreas
The routine monitoring of amylase and lipase values in otherwise asymptomatic patients treated with checkpoint blockade is not recommended. Similarly, corticosteroids are not indicated in patients with asymptomatic elevations in amylase/lipase without other symptoms of pancreatitis. Nevertheless, when pancreatitis is suspected clinically, amylase and lipase should be checked since immune-related pancreatitis has been reported in patients treated with CTLA-4 and PD-1 blockade. The high rate of asymptomatic elevations in amylase/lipase in clinical trials of patients receiving CTLA-4 and PD-1/PD-L1 blockade is of uncertain clinical significance since these patients did not meet the diagnostic criteria for pancreatitis.

Neurologic Syndromes
Neurologic syndromes have been associated with checkpoint blockade with ipilimumab. These include posterior reversible encephalopathy syndrome, encephalitis, aseptic meningitis, enteric neuropathy, and transverse myelitis. Cases of Guillain-Barre syndrome are particularly notable because one case resulted in a treatment-related death in a postsurgical adjuvant study of ipilimumab. As with other irAEs, corticosteroids can be helpful. In consultation with a neurologist, plasmapheresis and intravenous immunoglobulin may be considered.

Hematologic Syndromes
Red cell aplasia, neutropenia, and acquired hemophilia A have also been described in patients treated with ipilimumab, as has thrombocytopenia. Similar to many of the irAEs described above, the standard approach remains initial immunosuppression with corticosteroids. A bone marrow biopsy may be necessary in some cases, particularly when the diagnosis remains unclear.

IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH COMBINATION OF CONCURRENT CTLA-4 AND PD-1 BLOCKADE
The distinct action mechanisms of CTLA-4 and PD-1 blockade have led to investigations treating patients with both CTLA-4 and PD-1/PD-L1 in those who develop a variety of malignancies. Published data on the combination of ipilimumab and nivolumab exist for patients with advanced melanoma. The rate of published grade 3/4 treatment-related adverse events related to therapy in patients receiving this treatment is approximately 50%, which is numerically higher than rates described for patients receiving either CTLA-4 or PD-1/PD-L1 agents as single agents. Many grade 3/4 irAEs in this trial, however, were asymptomatic, abnormal laboratory values. This included a high rate of patients with asymptomatic elevations in lipase (over 10%), none of whom developed pancreatitis. No new toxicities were attributed to the combination of ipilimumab and nivolumab that have not been seen with ipilimumab or nivolumab alone.

The combination of ipilimumab and nivolumab may have a different safety profile in patients with other advanced malignancies, and this combination remains under active investigation. Other studies seek to test similar combinations using different CTLA-4 and PD-1/PD-L1–blocking antibodies (NCT01975831, NCT02089685, NCT01928394).

COMBINATION OF IMMUNE CHECKPOINT-BLOCKING ANTIBODIES AND TARGETED THERAPY
The treatment of many malignancies has improved with the discovery of oncogenic proteins amenable to targeted inhibi-
tion. One of these momentous advances has been targeting mutant \textit{BRAF} and the mitogen-activated protein (MAP) kinase pathway in patients with melanoma.\textsuperscript{57-62} Based on preclinical evidence that suggests \textit{RAF} inhibitors can have positive immunologic effects,\textsuperscript{63-68} there has been great interest in exploring combinations of targeted agents that inhibit mutant \textit{BRAF} with immune checkpoint-blocking antibodies.

The toxicity profile of combinations of targeted agents and immune-checkpoint blockade, however, is just beginning to be explored. In the only published prospective study, treatment with vemurafenib and ipilimumab was associated with a high rate of grade 3 transaminase elevations that required cessation of further exploration of this combination as concurrent therapy.\textsuperscript{69} Rash was also an important problem with this combination, which is consistent with similar findings when vemurafenib was administered soon after completing ipilimumab.\textsuperscript{70}

The irAE profile of ipilimumab in combination with \textit{RAF} inhibitors may vary by specific \textit{RAF} inhibitor. In a separate phase I study, dabrafenib was combined with ipilimumab and preliminarily, no major safety concerns with this doublet combination have been seen.\textsuperscript{71} The safety of ipilimumab with dabrafenib and trametinib, however, may be more problematic because some patients treated with this triplet had severe colitis with perforation.

Future investigations of targeted agents and immune checkpoint-blocking antibodies should continue in patients who develop multiple diseases, and that dose and schedule will be critical to the safety and possibly efficacy of these combination approaches. It is expected that combinations of targeted agents with PD-1/PD-L1 antibodies may show a more favorable side-effect profile than combinations with ipilimumab; however, this is the subject of ongoing investigation.

**COMBINATION OF IPILIMUMAB AND GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR**

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) (Leukine; Genzyme, Ridgefield, NJ) currently is not indicated to prevent or treat irAEs. Nonetheless, combining GM-CSF with immune-checkpoint blockade is of interest based on favorable preclinical data suggesting GM-CSF-secreting tumor vaccines enhanced the activity of CTLA-4 blockade.\textsuperscript{72} The combination of GM-CSF and ipilimumab was tested in patients with advanced melanoma in a phase II randomized study (ipilimumab 10 mg/kg plus GM-CSF vs. ipilimumab 10 mg/kg alone). Interim results indicate that the combination prolonged survival and was associated with fewer irAEs than ipilimumab 10 mg/kg alone.\textsuperscript{73}

Reasons for the decreased rate of side effects are unclear, but GM-CSF has been implicated in the pathogenesis of inflammatory bowel disease.\textsuperscript{74} Whether GM-CSF would result in similar effects in patients treated with the commercially available dose of ipilimumab (3 mg/kg) is unknown. Additional studies are necessary before GM-CSF is routinely recommended for patients being treated with ipilimumab.

**OPPORTUNISTIC INFECTIONS IN IMMUNOSUPPRESSED PATIENTS**

Since prolonged immune suppression is occasionally used to treat irAEs, patients can be at risk for unusual or opportunistic infections. Though anecdotal cases of these infections, such as \textit{Aspergillus} pneumonia, have been reported,\textsuperscript{75} the true incidence of these opportunistic infections remains unknown. \textit{Pneumocystis jiroveci} prophylaxis with cotrimoxazole, atovaquone, or pentamidine should be considered in patients treated with 20 mg of prednisone equivalent daily for at least 4 weeks, based on the National Comprehensive Cancer Network guidelines for the Prevention and Treatment of Cancer-Related Infections (Category 2B recommendation). The role of prophylactic antiviral or antifungal therapy in this setting is unclear.

**INVESTIGATIONS CORRELATING IMMUNE-RELATED ADVERSE EVENTS WITH EFFICACY**

The correlation between efficacy of checkpoint-blocking antibodies and the occurrence of irAEs is controversial.\textsuperscript{76,77} Patients can benefit from checkpoint-blocking antibodies without developing irAEs. Any potential association between PD-1/PD-L1 blockade and irAEs will be hard to determine as the incidence of significant irAEs is low.

**SAFETY OF IMMUNE-CHECKPOINT INHIBITION IN PATIENTS WITH UNDERLYING AUTOIMMUNE CONDITIONS**

The safety of immune-checkpoint inhibitors in patients with an unrelated autoimmunity disorder (e.g., rheumatoid arthritis, systemic lupus erythematosus) is unknown. Both CTLA-4 and PD-1 have an important function in maintaining immunologic homeostasis, and there is theoretic concern that therapeutic blockade of these receptors could lead to exacerbations of underlying autoimmune conditions. Preclinical models suggest CTLA-4 blockade can exacerbate autoimmune diseases.\textsuperscript{78,79} Since patients with underlying autoimmune conditions were not included in clinical trials of checkpoint-blocking antibodies, clinical evidence of the safety of this approach requires further study. Anecdotally, some patients with underlying autoimmune conditions have been treated safely with ipilimumab,\textsuperscript{80,81} but one patient with multiple sclerosis reported worsening symptoms after ipilimumab.\textsuperscript{82} Given the profound potential benefits of these checkpoint-blocking antibodies in patients with life-threatening malignancies, clinicians should engage patients with autoimmune diseases in thoughtful discussion about the possible benefits and risks of immunologic checkpoint blockade.

**CONCLUSION**

Immunologic-checkpoint inhibition targeting CTLA-4 and PD-1/PD-L1 has dramatically improved the care of patients
with many advanced malignancies. Treatment is associated with typically transient irAEs, but irAEs occasionally can be severe and fatal. Rapid identification of these side effects and initiation of systemic immunosuppression can improve outcomes without compromising the efficacy of immune-checkpoint inhibition. Although no prospective data exist to guide recommendations for the best specific immunosuppressive treatment, adherence to established guidelines based upon collective clinical experience is recommended. Clinical experience with immune-checkpoint inhibitors in a variety of disease settings and in novel combinations ultimately will refine knowledge and management of irAEs and provide the opportunity to obtain the full therapeutic potential of this promising treatment modality.

Disclosures of Potential Conflicts of Interest


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Blocking antibodies, designed to interfere with checkpoint molecules CTLA-4 and PD-1/PD-L1 and counteract these immune suppressive mechanisms, have shown significant success in promoting immune responses against cancer and can result in tumor regression in many patients. While inhibitors to CTLA-4 and the PD-1/PD-L1 axis are well-established for the clinical management of melanoma, many patients do not respond or develop resistance to these interventions. Side effects were managed with established safety guidelines and usually resolved within 3–4 weeks and the 3-year survival rate for patients who discontinued treatment was 67% (52).

Bispecific antibodies have also been generated which target checkpoint molecules directly. Common side effects of immune checkpoint inhibitors include rash, diarrhea, low thyroid hormone, and fatigue. But known side effects extend to inflammation of the lung, intestines or liver, hormonal abnormalities, and kidney, heart, or neurologic problems. Immune checkpoint inhibitors approved by the U.S. Food and Drug Administration (FDA) to help patients with a variety of cancers include Opdivo (nivolumab), Yervoy (ipilimumab), Keytruda (pembrolizumab), Bavencio (avelumab), and Tecentriq (atezolizumab).

“While novel immunotherapies allow for life-extending therapy for selected forms of cancer, their success is associated with potentially substantial toxicity,” said Robert W. Carlson, MD, chief executive officer of NCCN.