JAMA Oncology | Review

Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors
A Review

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IMPORTANCE The development of immune checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) has significantly improved the treatment of a variety of cancers and led to US Food and Drug Administration approvals for patients with a variety of malignant neoplasms. Immune checkpoint inhibitors enhance antitumor immunity by blocking negative regulators of T-cell function that exist both on immune cells and on tumor cells. Although these agents can lead to remarkable responses, their use can also be associated with unique immune-related adverse effects (irAEs).

OBSERVATIONS In general, use of PD-1 inhibitors such as nivolumab and pembrolizumab has a lower incidence of irAEs compared with those that block CTLA-4 such as ipilimumab. The combination of nivolumab and ipilimumab has a higher rate of irAEs than either approach as monotherapy. Consensus guidelines regarding the treatment of the most common irAEs including rash, colitis, hepatitis, endocrinopathies, and pneumonitis have been established. The mainstay of irAE treatment consists of immunosuppression with corticosteroids or other immunosuppressant agents such as infliximab; most irAEs will resolve with appropriate management.

CONCLUSIONS AND RELEVANCE The clinical use of immune checkpoint inhibitors is expanding rapidly. Oncology practitioners will therefore be required to recognize and manage irAEs in a growing patient population. Early recognition and treatment are essential to prevent patient morbidity and mortality, and adherence to established algorithms is recommended.

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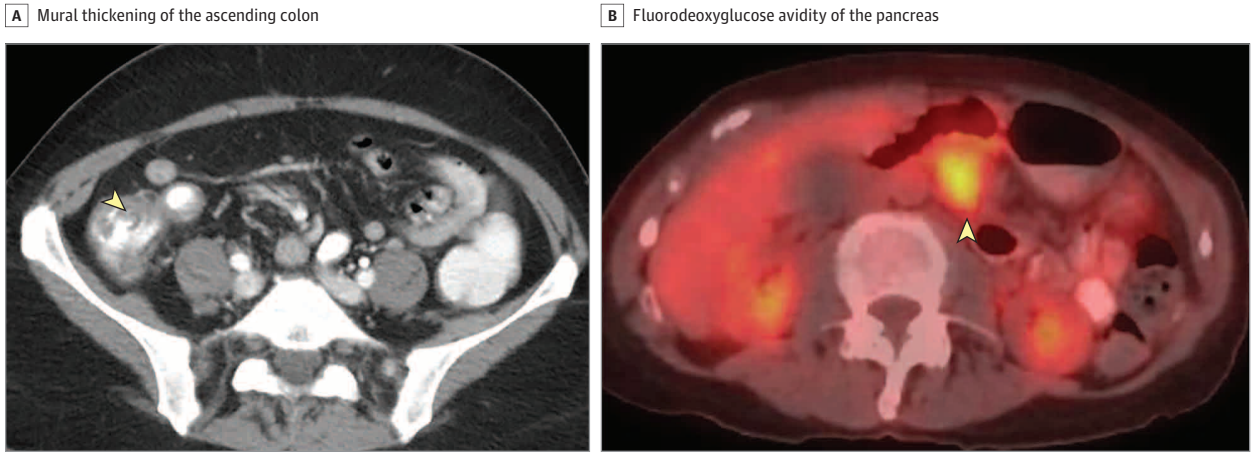
Immune checkpoint inhibitors enhance antitumor immunity by blocking negative regulators (checkpoints) of T cell function that exist on both immune and tumor cells. Although there are many T cell checkpoints that could be susceptible to this approach, 2 particular targets, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) have been most extensively evaluated in the clinic. Ipilimumab (anti–CTLA-4) is currently approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma,[1,2] and the PD-1–blocking antibodies nivolumab[3-5] and pembrolizumab[6-8] are both FDA approved for the treatment of metastatic melanoma and non–small cell lung cancer (NSCLC).[4,5,8] Nivolumab is also approved for the treatment of renal cell carcinoma.[9,10] Many other immune checkpoint inhibitors, such as those targeting the ligand for PD-1, PD-L1, are undergoing clinical investigation.[11]

Despite the effective antitumor immune response induced by these inhibitors, by blocking the negative regulators of immunity that are normally important for maintaining immunologic homeostasis, treatment can be associated with distinctive inflammatory adverse effects known as immune-related adverse events (irAEs). Immune-related adverse events are distinct both in mechanism and management from adverse effects commonly associated with chemotherapy.[12,13] In this review, we discuss the most common irAEs and provide suggestions for optimal treatment. We have elected to focus on data relevant to the FDA-approved antibodies targeting CTLA-4 (ipilimumab) in melanoma and PD-1 (nivolumab and pembrolizumab) in melanoma, NSCLC, and renal cell carcinoma, as these agents are most currently relevant to the clinic. We searched Medline for phase 2 and 3 studies of ipilimumab, nivolumab, and pembrolizumab within these indications to report the overall incidence of irAEs. In our discussion of treatment for specific irAEs, we incorporate relevant published case reports and retrospective series, as well as our own clinical experience.

The Overall Incidence and Clinical Importance of Immune-Related Adverse Events

The majority of data documenting irAEs come from large published trials, mostly in patients with advanced melanoma, NSCLC, and renal cell carcinoma. Additionally, reports of large patient cohorts from expanded access programs and retrospective analyses

Figure 1. Imaging Findings of an Immune-Related Adverse Effect



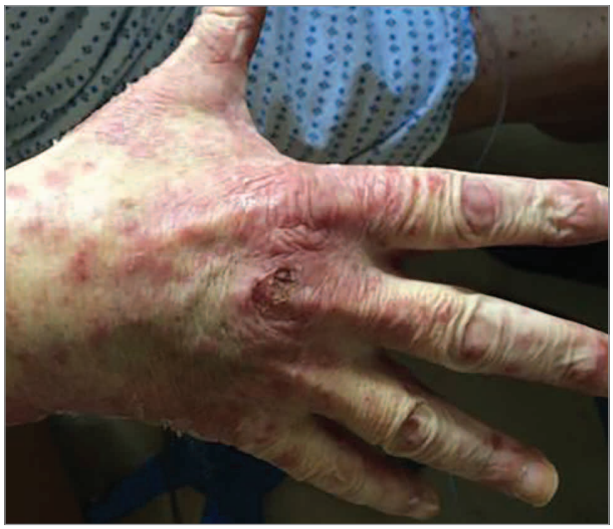
A, Mural thickening (arrowhead) of the ascending colon associated with diarrhea and abdominal pain. B, Fluorodeoxyglucose avidity (arrowhead) of the pancreas associated with elevated amylase and lipase levels but no clinical symptoms of pancreatitis.

have also provided information on the incidence of irAEs.[14,15] In general, PD-1 inhibitors have a lower incidence of irAEs compared with those that block CTLA-4 such as ipilimumab, whereas the combination of nivolumab and ipilimumab has a higher rate of irAEs than either approach as monotherapy. For example, in a phase 3 study in patients with advanced melanoma receiving nivolumab, ipilimumab, or the combination of both, grade 3/4 treatment-related adverse events were observed in 16% of patients treated with nivolumab, 27% of patients treated with ipilimumab, and 55% of patients treated with the combination.[16] Similar results were seen in a phase 3 study of pembrolizumab vs ipilimumab in patients with melanoma, with lower rates of grade 3/4 adverse events in patients receiving pembrolizumab.[7] The incidence of grade 3/4 irAEs from PD-1–blocking antibodies alone does not appear to significantly vary among patients with different tumor types, with grade 3/4 rates of less than 20%.[4,8-10] Fortunately, despite the rate of grade 3/4 adverse events, irAEs that lead to treatment-related death are rare, 2% or less.[4,17]

Management of Common Immune-Related Adverse Events

The optimal management of irAEs is based on clinical experience because no prospective trials have been conducted to evaluate the best irAE treatment strategy. Nevertheless, based primarily on the experience in patients with melanoma receiving ipilimumab, consensus management regarding the treatment of the common irAEs including rash, colitis, hepatitis, endocrinopathies, and pneumonitis has been established.[18] The mainstay of irAE treatment consists of immunosuppression with corticosteroids or other immunosuppressant agents such as infliximab. Fortunately, with appropriate management, most irAEs resolve,[19] and temporary immunosuppression to treat an irAE does not seem to limit the efficacy of immune checkpoint inhibition.[14,17] In patients who require a prolonged course of corticosteroids to resolve their symptoms (20 mg of prednisone or equivalent daily for ≥4 weeks), *Pneumocystis carinii* pneumonia prophylaxis should be considered as per National Comprehensive Cancer Network guidelines.[20]

Figure 2. Physical Examination Findings of an Immune-Related Adverse Effect



Erythematous maculopapular rash located on the hand.

In this section, we review the current literature related to the most common irAEs in patients treated with immune checkpoint inhibitors. In clinical practice, the majority of treatment decisions should be driven by patient-reported symptoms, although there are some laboratory and imaging correlates for irAEs (**Figures 1** and **2**).[21]

Rash and/or Pruritus

The most common irAE associated with checkpoint inhibitor use is rash and/or pruritus. Nearly 50% of patients treated with ipilimumab will experience this irAE.[12] Rash is also one of the most common toxic effects of anti–PD-1 therapy, occurring in approximately 40% of patients treated with nivolumab or pembrolizumab alone and in approximately 60% of patients treated with the combina-

tion of ipilimumab and nivolumab.[16,22] Fortunately, the rate of grade 3/4 rash with these agents remains low, at less than 10%.[7,23]

Rashes typically appear faintly erythematous, reticular, and maculopapular and are located across the limbs and trunk.[24] These immune-related rashes can frequently begin within the first 2 weeks of therapy and can be seen in patients with any tumor type.[25,26] Less common dermatologic toxic effects such as bullous pemphigoid and Sweet syndrome have also been described.[27,28]

The initial approach for dermatologic toxic effects is supportive. Topical corticosteroid creams of medium to high potency can be used for rash.[29] Cold compresses, oatmeal baths, and topical corticosteroids may be helpful in relieving symptoms of pruritus in addition to systemic antihistamines such as diphenhydramine hydrochloride and hydroxyzine hydrochloride. Oral or topical doxepin hydrochloride, a tricyclic antidepressant, has also been used with some success for pruritic symptoms[30] as has oral aprepitant.[29] Anti–CTLA-4 or anti–PD-1 therapy can be continued while managing grade 1 to 2 skin toxic effects. Severe rash (grade 3 or higher) should be treated with oral corticosteroids, usually at an equivalent dose of prednisone 1-mg/kg daily. In these cases of more severe rash, treatment with additional immunotherapy should be delayed until symptoms improve to baseline or grade 1 or lower. In the event of severe rashes, not initially responsive to oral corticosteroids, clinicians should consider the addition of immunosuppressive medications such as infliximab, mycophenolate mofetil, or cyclophosphamide. Treatment with immune checkpoint inhibitors should be discontinued if cutaneous symptoms fail to improve after 12 weeks of supportive management due to the risk of more severe symptoms.

Rarely, Stevens-Johnson syndrome/toxic epidermal necrolysis has been reported.[31] In these case reports, management is reliant on a multispecialty approach with dermatology and critical care evaluation. Patients require hospitalization for supportive management with intravenous fluids and electrolyte replacement. Higher-dose oral corticosteroids, such as prednisone 1- to 2-mg/kg daily or methylprednisolone 1- to 4-mg/kg daily, can be considered in severe cases.[12] In cases of Stevens-Johnson syndrome/toxic epidermal necrolysis, treatment with the precipitating immune checkpoint inhibitor should be permanently discontinued.

Mucosal toxic effects, such as mucositis, gingivitis, and sicca syndrome have also been described, particularly with the anti–PD-1 agents. Symptoms can be managed with supportive care including oral rinses with topical steroid, viscous lidocaine hydrochloride, and good oral hygiene.[24]

Vitiligo is another cutaneous irAE that usually occurs at least 3 weeks after initiation of immune checkpoint inhibitor therapy. Vitiligo frequently occurs over the upper extremities and is observed in a greater number of patients treated with the anti–PD-1 agents, such as pembrolizumab (<10%) compared with ipilimumab (2%).[7] No definitive treatment exists for immune therapy–related vitiligo. The development of vitiligo may be associated with favorable treatment benefit in patients treated with pembrolizumab,[32,33] as it has been described with other immunotherapy agents,[34] but this requires further study.

Diarrhea and/or Colitis

Diarrhea and/or colitis is commonly seen in patients treated with checkpoint inhibitors. The incidence of grade 3/4 colitis is higher among patients treated with the CTLA-4–blocking antibodies (7%) compared with those targeting PD-1 (1.8%).[7] Moreover, the rate of grade 3/4 diarrhea with the combination of ipilimumab and nivolumab is not significantly higher than that in patients treated with either antibody alone (6.1% for ipilimumab vs 2.2% for nivolumab vs 9.3% for the combination).[16]

Although time of onset can vary, the median time to onset of diarrhea in patients treated with ipilimumab or the combination of ipilimumab and nivolumab is 6 to 8 weeks after the initiation of therapy.[22] Sometimes radiographic changes can be seen on computed tomography scan such as mild diffuse bowel thickening or segmental colitis associated with diverticulosis, which is characterized by segmental moderate wall thickening in a segment of preexisting diverticulosis.[35] Diarrhea from checkpoint inhibitor therapy is believed to arise as a result of underlying colonic inflammation (colitis). Nevertheless, in clinical trials, diarrhea is often reported separately from colitis as per definitions by the Common Terminology Criteria for Adverse Events based on patient symptoms. Clinicians should be aware that diarrhea and colitis are typically treated similarly.

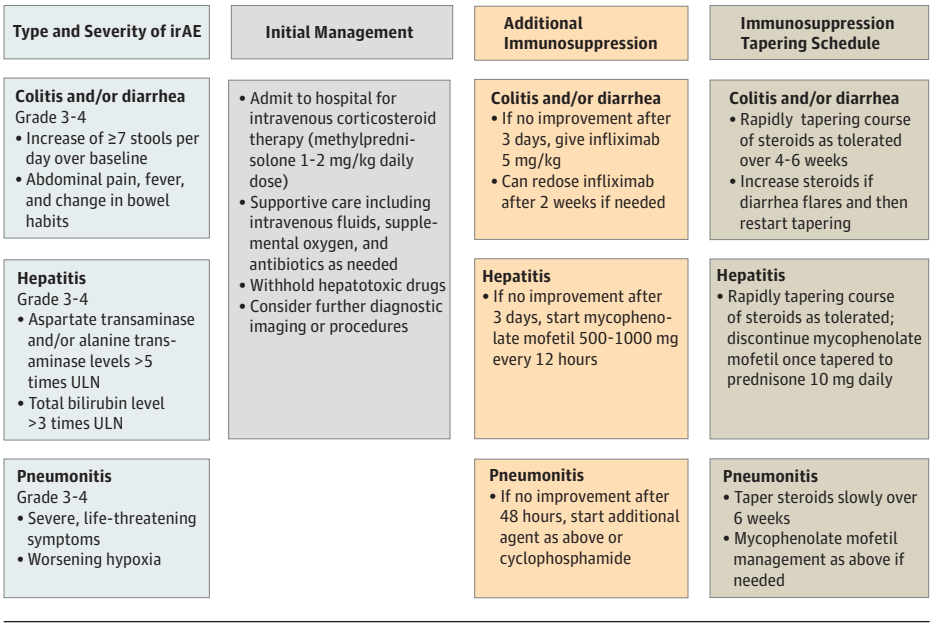
When patients present with diarrhea, the first step in management should always to be to assess for etiologies other than irAEs, such as infection with *Clostridium difficile* or other bacterial or viral pathogens. Antidiarrheal agents, such as loperamide hydrochloride, diphenoxylate hydrochloride, or atropine sulfate, can be used up to 4 times daily in mild cases. For patients who have a minimal increase in bowel movements over baseline that persists, budesonide (9 mg daily) can also be used. If symptoms persist (>3 days), present with at least moderate intensity, or there is imaging consistent with colonic inflammation, oral (prednisone 1- to 2-mg/kg daily) or intravenous corticosteroid treatment (methylprednisolone up to 2 mg/kg twice a day) should be implemented.[26] In severe cases, hospitalization may be necessary for administration of intravenous fluids and electrolyte replacement. For severe and/or steroid-refractory symptoms, infliximab (an anti–tumor necrosis factor agent), at a dose of 5 mg/kg once every 2 weeks, has been used with success (**Figure 3**)[36-38] based on data from patients with inflammatory bowel disease.[39] Many times a colonoscopy is considered, but in our experience this rarely changes management and should only be performed if the diagnosis remains unclear. Treatment with additional immune checkpoint inhibition should be held until symptoms resolve to grade 1 or less.

Development of diarrhea and/or colitis during use of 1 checkpoint inhibitor does not necessarily prohibit the use of another. For example, patients who experienced colitis from ipilimumab therapy did not have recurrence of symptoms while taking nivolumab.[40] Mortality associated with treatment-related diarrhea and/or colitis is usually a result of delayed recognition of symptoms or delayed and/or nonadherence to treatment.[41] Fortunately, given the increased awareness and recognition of colitis, there have been no deaths from colitis in any recently published trials.[16,19] There is no treatment that has been shown to prevent immune checkpoint inhibitor–related diarrhea. Budesonide was tested as a prophylactic agent, but unfortunately it did not significantly reduce the incidence of diarrhea.[42]

Hepatitis

Hepatitis related to checkpoint inhibition is associated with elevations in levels of aspartate transaminase, alanine transaminase, and occasionally bilirubin. Hepatitis can occur at any time but generally

Figure 3. Treatment of Severe and Steroid-Refractory Immune-Related Adverse Effects (irAEs)



This figure is based on published management algorithms but also incorporates our clinical experience at Memorial Sloan Kettering Cancer Center. ULN indicates upper limit of normal.

begins 8 to 12 weeks after the initiation of checkpoint inhibitor therapy. In most cases the hepatitis is asymptomatic.[22,43] Immune-related hepatotoxic effects of all grades are more frequently reported in patients treated with CTLA-4–blocking antibodies (but still <10%) compared with patients treated with PD-1–blocking antibodies.[23,44] Combination therapy with anti–CTLA-4 and anti–PD-1 inhibition is associated with a higher incidence of hepatotoxic effects than either single-antibody approach.[16] Immunomodulatory medications, such as prednisone, can be effective in patients with hepatitis, and the median time to resolution is typically approximately 8 weeks.[19]

Hepatic function should be monitored before each dose of checkpoint inhibition, and if elevated, viral and other drug-induced causes of hepatitis should be excluded. No characteristic radiographic finding is associated with checkpoint inhibition hepatitis; however, in severe cases periportal edema or hepatomegaly may be observed.[43] As with treating other irAEs, if no other immediate cause is obvious, prompt treatment with corticosteroids (prednisone 1- to 2-mg/kg/d or methylprednisolone 0.5 to 1-mg/kg/d) is recommended. In rare cases, elevations in aspartate transaminase and alanine transaminase are steroid refractory and mycophenolate mofetil (500-1000 mg every 12 hours) or tacrolimus may provide benefit. Unlike other gastrointestinal irAEs such as colitis/diarrhea, infliximab is contraindicated in cases of hepatitis due to an increased risk of hepatotoxic effects with infliximab therapy itself. A protracted course may require multiple cycles (of ≥3 weeks) of systemic steroids with or without additional immunosuppressive medications.[43] In a highly refractory case with rapid clinical decompensation, antithymocyte globulin 1.5-mg/kg for 2 consecutive days has been added to steroids and mycophenolate mofetil with some success.[45] Hepatic toxic effects may take more than 1 month to resolve and can result in permanent discontinuation of checkpoint inhibitor use in the event of persistent grade 3/4 hepatitis. For grade 1/2 treatment-related hepatitis, therapy should be delayed and liver function test monitoring increased, but treatment can be resumed provided resolution of transaminitis to grade 1 or lower occurs. Some patients may have a rebound increase of their liver function test values. It is important to ensure that these values remain normal, even after completion of immunosuppression and apparent resolution.

Endocrinopathy

Whereas the aforementioned irAEs usually have straightforward presentation, the diagnosis of endocrinopathies associated with checkpoint inhibition can be more challenging. Patients may present with nonspecific symptoms, including fatigue, nausea, headache, and depression; therefore, practitioners must be vigilant. Hypophysitis (pituitary inflammation) and hypothyroidism are the most common endocrinopathies and are believed to occur in up to 10% of patients treated with CTLA-4 inhibition.[46,47] Case reports of autoimmune insulin-dependent diabetes have also been reported in the literature.[48] The frequency of endocrinopathy in patients treated with anti–PD-1 agents is less well known but appears to be lower, at less than 1% in patients with advanced melanoma[7,16] and up to 6.9% in patients with NSCLC.[8] It is possible that rates of significant endocrinopathy vary slightly from trial to trial based on differences in protocol-required evaluations, which may have led to different levels of diagnostic sensitivity.

Typically, hypophysitis is diagnosed by means of clinical symptoms of fatigue, headache, hypogonadism (amenorrhea or impotence), hypotension, hypoglycemia, and radiographic findings (enhancement and enlargement of the pituitary on brain magnetic resonance imaging[49,50]). Biochemical evidence of pituitary dysfunction (low adrenocorticotropic hormone and thyrotropin and occasionally low luteinizing hormone, follicle-stimulating hormone, growth hormone, and/or prolactin levels) is often noted in peripheral blood assessments.

An important distinction for endocrinologic toxic effects is that unlike other irAEs that typically completely resolve with appropriate treatment, immune checkpoint inhibitor–related endocrinopathy usually requires permanent hormone replacement. For patients who present with acute symptoms, some clinicians have described a course of high-dose corticosteroids (prednisone 1- to 2-mg/kg daily) that may be effective in reversing the inflammatory process and preventing long-term hormone deficiency in rare cases. Gonadal function in some men has recovered.[49] Nonetheless, given the potential for permanent hypothalamic-pituitary-gonadal dysfunction, patients of childbearing age should be counseled appropriately on the possibility of immune checkpoint inhibitor use affecting future fertility.

Because routine monitoring of thyroid function with a thyrotropin laboratory evaluation is required prior to each dose of ipilimumab and the combination of ipilimumab and nivolumab, patients receive a diagnosis of thyroid function abnormalities (hyperthyroidism or hypothyroidism) before they are symptomatic. Hyperthyroidism can be managed with a β-blocker and steroids (if acute thyroiditis is present).[51] Hypothyroidism occurs more commonly than hyperthyroidism and is managed with replacement doses of thyroid hormone.

The most severe endocrinopathy is acute adrenal insufficiency or adrenal crisis. Stress dose steroids should be used in the event that adrenal crisis is suspected. Hospitalization is required to manage the symptoms of severe dehydration, electrolyte abnormalities (hyperkalemia and hyponatremia), hypotension, and/or shock. In isolated cases, patients have been able to wean from steroids over time, but in our experience this is the exception.[52] Patients receiving long-term hydrocortisone supplementation for secondary hypoadrenalism will need an increase in their steroid dose when undergoing medically stressful scenarios such as a planned surgical procedure or an infection. We recommend consultation and ongoing care with an endocrinologist in these situations.

Pneumonitis

Pneumonitis is a rare (<10%) but potentially life-threatening irAE seen in patients treated with CTLA-4– and PD-1–blocking antibodies.[3,6,7,16,53,54] Although it may occur at any time, the appearance of pneumonitis tends to occur later than other irAEs, most commonly several months after treatment is initiated. The incidence of pneumonitis is higher in patients receiving anti–PD-1 therapy compared with ipilimumab therapy, but rates of grade 3/4 adverse events are fortunately low in patients receiving both classes of drugs, alone or in combination.[7,17] The rate of grade 3/4 pneumonitis secondary to treatment with pembrolizumab or nivolumab is similar across tumor types; however, there have been more treatment-related deaths due to pneumonitis in patients with NSCLC.[4,55]

Any patient presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia (pulse oximetry, <90%) should be assessed with cross-sectional imaging. Computed tomography findings consistent with pneumonitis include bilateral consolidative and ground glass opacities predominantly in peripheral distribution, mimicking the cryptogenic organizing pneumonia pattern; and ground glass opacities with interlobular septal thickening in basilar and peripheral distribution, mimicking the nonspecific interstitial pneumonia pattern.[21,56]

In mild to moderate cases, oral steroid treatment including prednisone 1- to 2-mg/kg daily or methylprednisolone 0.5- to 1-mg/kg daily should be initiated. In moderate to severe cases, a bronchoscopy should be performed to exclude infectious etiologies before starting immunosuppression. In severe cases, the patient should be hospitalized and treatment should consist of high doses of corticosteroids (ie, methylprednisolone 2- to 4-mg/kg/d) and additional immunosuppression, including mycophenolate mofetil, cyclophosphamide, and infliximab can be administered. No further doses of immune checkpoint inhibition should be administered after moderate to severe cases.[56]

In addition to pneumonitis, other pulmonary manifestations of inflammatory conditions have been observed including sarcoidosis.[57,58] These conditions are evaluated and treated similarly to pneumonitis.

Management of Less Common Immune-Related Adverse Events

Although the skin, bowel, liver, endocrine system, and lung are more commonly affected by immune checkpoint–blocking antibodies, other rare irAEs can occur and affect the pancreas, bone marrow, and neurologic system. In this section, we share our experience and the experience described in the literature regarding these less common irAEs.

Pancreatitis

Pancreatitis is defined as the presence of 2 of the following 3 features: clinical symptoms, radiographic findings of an inflamed pancreas, or elevated pancreas enzyme levels (amylase and lipase).[59] In clinical trials, pancreatitis has been rarely reported with immune checkpoint inhibition.[60] When patients have a clinical diagnosis of pancreatitis, other etiologies such as malignant pancreatic/biliary obstructive processes, alcohol-related pancreatitis, and gallstone disease should be excluded. Once immune checkpoint antibody–related pancreatitis is diagnosed, patients can be successfully treated with prednisone 1 mg/kg tapered over several weeks once symptoms abate.

In many trials of immune checkpoint inhibitors, patients had asymptomatic elevations in amylase and/or lipase levels.[61-64] In most of these cases, however, patients with elevated laboratory values did not meet criteria for clinical pancreatitis. Because the clinical relevance of these asymptomatic elevations remains unclear, we do not advocate for steroid immunosuppression when only amylase and/or lipase values are elevated in the absence of symptoms or radiographic findings. We therefore only recommend checking these values in patients who are otherwise suspected of having pancreatitis on clinical grounds. This helps avoid false-positive diagnoses of pancreatitis, a problem compounded by the inherently nonspecific nature of elevated amylase and lipase values.[65]

Hematologic Toxicities

Hematologic irAEs occur occasionally, and severity varies from mild, asymptomatic cytopenias to more significant reports of immune thrombocytic purpura, autoimmune hemolytic anemia, acquired hemophilia, and disseminated intravascular coagulopathy.[66,67]

Anemia is described in less than 5% of patients treated with ipilimumab and in less than 10% of patients treated with PD-1 inhibitors. However, neutropenia[68] and pure red cell aplasia[69] have also been reported in the literature. A complete blood cell count should be performed prior each dose administration. Similarly to all other irAEs, early diagnosis is crucial.

Resolution typically occurs with discontinuation of immune checkpoint inhibition and supportive management with corticosteroids (the equivalent of prednisone 1-mg/kg daily) and transfusion of blood product as needed. However, in isolated cases in which cytopenias are refractory to treatment cessation and steroid therapy, patients have improved after administration of intravenous immunoglobulin with or without additional immunosuppressive agents, such as cyclosporine.[63,66,68] Following mild hematologic abnormalities, patients can generally continue immune checkpoint inhibition with close observation.

Neurologic Toxic Effects

Treatment with immune checkpoint inhibition occasionally results in neurologic toxic effects (<5%) of varying severity.[70] Neurologic irAEs may range from sensory neuropathies, such as paresthesias,[71] to more severe toxic effects such as aseptic meningitis, temporal arteritis,[72] a myasthenia gravis–like syndrome,[73,74] and Guillain-Barré syndrome.[71] Guillain-Barré syndrome is particularly notable given that it led to 1 patient death in an adjuvant study of ipilimumab therapy.[70,71,75]

Given the potential for severe adverse effects, early recognition of neurologic irAEs is important.[12] For diagnosis, lumbar puncture may be helpful. Findings such as a high white blood cell count (particularly with a high lymphocyte proportion) can point to an immune-mediated etiology. In these cases, the initiation of high-dose corticosteroid treatment (such as methylprednisolone 2-mg/kg) and/or plasmapheresis may halt and reverse neurologic complications.[71] Unfortunately, treatment with steroids is not universally effective and some patients may require intravenous immunoglobulin or supportive medications, such as pyridostigmine bromide, in the case of myasthenia gravis–like disease.[70,71] After a patient experiences a severe (grade 3 or 4) neurologic toxic effect, immune checkpoint inhibitor use should be permanently discontinued.[62,75]

Conclusions

Immune checkpoint inhibitors have already been FDA approved to treat patients with melanoma, NSCLC, and renal cell carcinoma. Many additional checkpoint-blocking agents are currently undergoing clinical evaluation, and it is likely that this class of drugs will play an increasingly important role for patients with many types of solid and hematologic malignant neoplasms. Oncology practitioners will therefore be required to recognize and manage irAEs in a growing patient population. Adherence to established algorithms is recommended, and as experience with these agents grows, it is imperative that practitioners report new or rare irAEs. Ideally, prospective studies should be conducted to test different immunosuppressive management strategies.

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Critical revision of the manuscript for important intellectual content: Friedman, Postow.
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REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.

2. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-2526.

3. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.

4. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol*. 2015;33(18):2004-2012.

5. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135.

6. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.

7. Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532.

8. Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.

9. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.

10. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33(13):1430-1437.

11. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387(10031):1909-1920.

12. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30(21):2691-2697.

13. Fecher LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its toxicities: a multidisciplinary approach. *Oncologist*. 2013;18(6):733-743.

14. Horvat TZ, Adel NG, Dang T-O, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma

treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*. 2015;33(28):3193-3198.

15. Altomonte M, Di Giacomo A, Queirolo P, et al. Clinical experience with ipilimumab 10 mg/kg in patients with melanoma treated at Italian centres as part of a European expanded access programme. *J Exp Clin Cancer Res*. 2013;32:82.

16. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.

17. Weber JS, Antonia SJ, Topalian SL, et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. *J Clin Oncol*. 2015;33(15 suppl):abstr 9018.

18. US Food and Drug Administration. Yervoy (ipilumab) Risk Evaluation and Mitigation Strategy (REMS). 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377_REMS.pdf. Accessed November 17, 2015.

19. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017.

20. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed June 2, 2016.

21. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic profiling of immune-related adverse events in advanced melanoma patients treated with ipilimumab. *Cancer Immunol Res*. 2015;3(10):1185-1192.

22. Hodi FS, Postow MA, Chesney JA, et al. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. *J Clin Oncol*. 2015;33(15 suppl):abstr 9004.

23. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020-1030.

24. Lacouture ME, Wolchok JD, Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol*. 2014;71(1):161-169.

25. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol*. 2013;69(3):e121-e128.

26. Postow MA. Managing immune checkpoint-blocking antibody side effects. *Am Soc Clin Oncol Educ Book*. 2015;35:76-83.

27. Pintova S, Sidhu H, Friedlander PA, Holcombe RF. Sweet's syndrome in a patient with metastatic melanoma after ipilimumab therapy. *Melanoma Res*. 2013;23(6):498-501.

28. Carlos G, Anforth R, Chou S, Clements A, Fernandez-Peñas P. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. *Melanoma Res*. 2015;25(3):265-268.

29. Lacouture ME. Management of dermatologic toxicities. *J Natl Compr Canc Netw*. 2015;13(5)(suppl):686-689.

30. Choi JN. How to recognize and manage ipilimumab-induced dermatologic adverse events. *ASCO Post*. 2013;42013. http://www.ascopost.com/issues/october-15-2013/how-to-recognize-and-manage-ipilimumab-induced-dermatologic-adverse-events.aspx. Accessed November 17, 2015.

31. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011. http://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed March 13, 2016.

32. Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol*. 2016;152(1):45-51.

33. Lo JA, Fisher DE, Flaherty KT. Prognostic significance of cutaneous adverse events associated with pembrolizumab therapy. *JAMA Oncol*. 2015;1(9):1340-1341.

34. Teulings H-E, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol*. 2015;33(7):773-781.

35. Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab-associated colitis: CT findings. *AJR Am J Roentgenol*. 2013;200(5):W468-74.

36. Pagès C, Gornet JM, Monsel G, et al. Ipilimumab-induced acute severe colitis treated by infliximab. *Melanoma Res*. 2013;23(3):227-230.

37. Merrill SP, Reynolds P, Kalra A, Biehl J, Vandivier RW, Mueller SW. Early administration of infliximab for severe ipilimumab-related diarrhea in a critically ill patient. *Ann Pharmacother*. 2014;48(6):806-810.

38. Minor DR, Chin K, Kashani-Sabet M. Infliximab in the treatment of anti-CTLA4 antibody (ipilimumab) induced immune-related colitis. *Cancer Biother Radiopharm*. 2009;24(3):321-325.

39. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther*. 2014;39(12):1349-1362.

40. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol*. 2013;31(34):4311-4318.

41. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer*. 2013;119(9):1675-1682.

42. Weber J, Thompson JA, Hamid O, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res*. 2009;15(17):5591-5598.

43. Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. *Invest New Drugs*. 2013;31(4):1071-1077.

44. Bernardo SG, Moskalenko M, Pan M, et al. Elevated rates of transaminitis during ipilimumab therapy for metastatic melanoma. *Melanoma Res*. 2013;23(1):47-54.

45. Chmiel KD, Suan D, Liddle C, et al. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. *J Clin Oncol*. 2011;29(9):e237-e240.

46. Corsello SM, Barnabei A, Marchetti P, De Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. *J Clin Endocrinol Metab*. 2013;98(4):1361-1375.

47. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. *Endocr Relat Cancer*. 2014;21(2):371-381.

48. Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. *Cancer Immunol Immunother*. 2015;64(6):765-767.

49. Blansfield JA, Beck KE, Tran K, et al. Cytotoxic T-lymphocyte-associated antigen-4 blockage can induce autoimmune hypophysitis in patients with metastatic melanoma and renal cancer. *J Immunother*. 2005;28(6):593-598.

50. Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary*. 2010;13(1):29-38.

51. Yu C, Chopra IJ, Ha E. A novel melanoma therapy stirs up a storm: ipilimumab-induced thyrotoxicosis. *Endocrinol Diabetes Metab Case Rep*. 2015;2015:140092.

52. Sarnaik AA, Yu B, Yu D, et al. Extended dose ipilimumab with a peptide vaccine: immune correlates associated with clinical benefit in patients with resected high-risk stage IIIc/IV melanoma. *Clin Cancer Res*. 2011;17(4):896-906.

53. Hamid O, Schmidt H, Nissan A, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. *J Transl Med*. 2011;9:204.

54. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.

55. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab vs docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.

56. Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med*. 2015;373(3):288-290.

57. Berthod G, Lazor R, Letovanec I, et al. Pulmonary sarcoid-like granulomatosis induced by ipilimumab. *J Clin Oncol*. 2012;30(17):e156-e159.

58. Barjaktarevic IZ, Qadir N, Suri A, Santamauro JT, Stover D. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. *Chest*. 2013;143(3):858-861.

59. Banks PA, Bollen TL, Dervenis C, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111.

60. Alabed YZ, Aghayev A, Sakellis C, Van den Abbeele AD. Pancreatitis secondary to anti-programmed death receptor 1 immunotherapy diagnosed by FDG PET/CT. *Clin Nucl Med*. 2015;40(11):e528-e529.

61. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133.

62. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33(18):2092-2099.

63. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.

64. Di Giacomo AM, Danielli R, Guidoboni M, et al. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother*. 2009;58(8):1297-1306.

65. Gullo L. Day-to-day variations of serum pancreatic enzymes in benign pancreatic hyperenzymemia. *Clin Gastroenterol Hepatol*. 2007;5(1):70-74.

66. Ahmad S, Lewis M, Corrie P, Iddawela M. Ipilimumab-induced thrombocytopenia in a patient with metastatic melanoma. *J Oncol Pharm Pract*. 2012;18(2):287-292.

67. Delyon J, Mateus C, Lambert T. Hemophilia A induced by ipilimumab. *N Engl J Med*. 2011;365(18):1747-1748.

68. Akhtari M, Waller EK, Jaye DL, et al. Neutropenia in a patient treated with ipilimumab (anti-CTLA-4 antibody). *J Immunother*. 2009;32(3):322-324.

69. Gordon IO, Wade T, Chin K, Dickstein J, Gajewski TF. Immune-mediated red cell aplasia after anti-CTLA-4 immunotherapy for metastatic melanoma. *Cancer Immunol Immunother*. 2009;58(8):1351-1353.

70. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. *Neuro Oncol*. 2014;16(4):589-593.

71. Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barré syndrome in a melanoma patient. *Ann Oncol*. 2011;22(4):991-993.

72. Bertrand A, Kostine M, Barnetche T, Truchetet M-E, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. *BMC Med*. 2015;13(1):211.

73. Loochtan AI, Nickolich MS, Hobson-Webb LD. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. *Muscle Nerve*. 2015;52(2):307-308.

74. Johnson DB, Saranga-Perry V, Lavin PJM, et al. Myasthenia gravis induced by ipilimumab in patients with metastatic melanoma. *J Clin Oncol*. 2015;33(33):e122-e124.

75. Eggermont AMM, Chiarion-Sileni V, Grob J-J, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16(5):522-530.