REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

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N Engl J Med 2018;378:158-68.
DOI: 10.1056/NEJMra1703481

Immunotherapy enhances a patient's immune system to fight disease and has recently been a source of promising new cancer treatments. Among the many immunotherapeutic strategies, immune checkpoint blockade has shown remarkable benefit in the treatment of a range of cancer types. Immune checkpoint blockade increases antitumor immunity by blocking intrinsic downregulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). Several immune checkpoint–directed antibodies have increased overall survival for patients with various cancers and are approved by the Food and Drug Administration (Table 1).

By increasing the activity of the immune system, immune checkpoint blockade can have inflammatory side effects, which are often termed immune-related adverse events. Although any organ system can be affected, immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver.[1] Less often, the central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved. The wide range of potential immune-related adverse events requires multidisciplinary, collaborative management by providers across the clinical spectrum (Fig. 1).

No prospective trials have defined strategies for effectively managing specific immune-related adverse events; thus, clinical practice remains variable. Nevertheless, several professional organizations are working to harmonize expert consensus on managing specific immune-related adverse events. In this review, we focus on 10 essential questions practitioners will encounter while caring for the expanding population of patients with cancer who are being treated with immune checkpoint blockade (Table 2).

Why Do Immune-Related Adverse Events Occur?

The precise pathophysiology underlying immune-related adverse events is unknown but is believed to be related to the role that immune checkpoints play in maintaining immunologic homeostasis (Fig. 2). CTLA-4 inhibits an immune response in several ways, including attenuating T-cell activation at a proximal step in the immune response.[2] In contrast, PD-1 is generally believed to inhibit T cells at later stages of the immune response in peripheral tissues.[3,4] The distinct functions of CTLA-4 and PD-1 are reflected in the different toxicity seen in knockout mouse models. Mice lacking the CTLA-4 gene die from lymphoproliferation,[5,6] whereas mice lacking PD-1 have more limited and variable, model-dependent autoimmunity, including arthritis and cardiomyopathy.[7]

Similarly, patients who are treated with anti–CTLA-4 therapy have immune-related adverse events that differ from those in patients treated with anti–PD-1,

and the effects of anti–CTLA-4 therapy are generally more severe.[8-10] For example, colitis and hypophysitis seem to be more common with anti–CTLA-4 therapy, whereas pneumonitis and thyroiditis appear to be more common with anti–PD-1 therapy.[11-14] Although it is not yet known why organ-specific toxic effects differ between these two targets, reports of hypophysitis have identified the expression of CTLA-4 on normal pituitary cells, which may contribute to the toxicity of anti–CTLA-4 therapy.[15,16] In contrast, thyroid disorders can occur in patients receiving anti–PD-1 therapy who have antithyroid antibodies, whether they are present at baseline or detectable only after treatment initiation. It may be that in addition to T-cell–mediated immunity, anti–PD-1 or anti–PD-L1 treatment modulates humoral immunity, enhancing preexisting antithyroid antibodies.[14] Another implication is that PD-1 may be involved in maintaining self-tolerance, the process that keeps the immune system from attacking the person it was designed to protect.

The extent to which autoantibodies rather than autoreactive T cells contribute to immune-related adverse events remains unknown and may differ among toxic effects. In a report of two cases of myocarditis, T-cell infiltration of the myocardium was evident, and no B cells or antibody deposits were identified.[17] Similar T-cell clones were found in both the myocardium and the tumor in one patient, leading to speculation that this T-cell population may have been reactive against an antigen shared between normal tissue (myocardium) and tumor. Vitiligo, a depigmentation disorder caused by an autoimmune attack on melanocytes, is also frequently seen in patients with melanoma who are treated with immune checkpoint blockade, a finding suggestive of cross-reactivity between T cells directed against a tumor and T cells directed against a related antigen in normal tissue.[18]

In addition, cytokines may be involved in the pathophysiology of immune-related adverse events. One study identified elevated levels of interleukin-17 in patients with ipilimumab-induced colitis,[19] and interleukin-17 elevations have been observed in preclinical models of colitis.[20] These findings raise the possibility of using interleukin-17 blockade as a strategy for treating colitis induced by immune checkpoint blockade, although there is also a theoretical risk in reversing the favorable antitumor effects of immune checkpoint

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

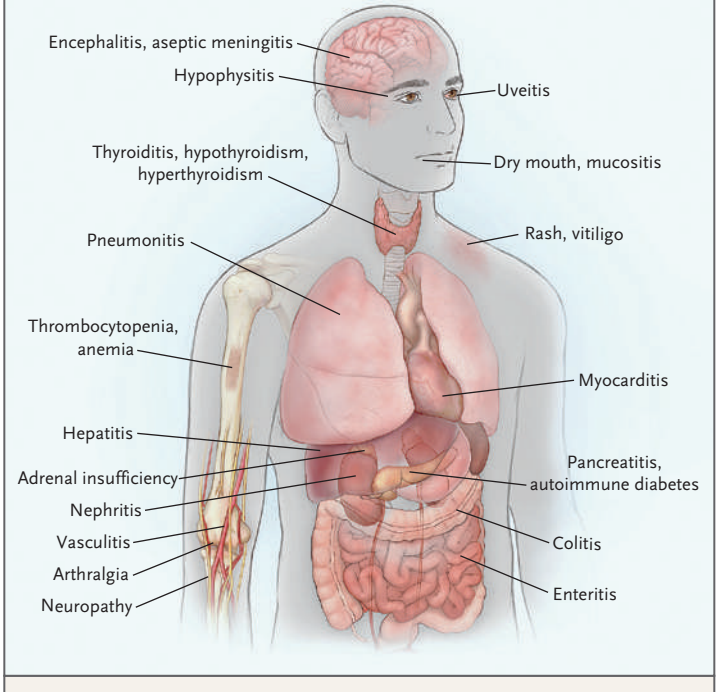

Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Table 2. Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti–CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti–PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.
Is it necessary to restart treatment after resolution of an adverse event?	Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.
Is it safe to treat patients at potentially increased risk for such adverse events?	Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.

blockade, as described in a report on one case.[21] Several antibodies that block interleukin-17, such as secukinumab, ixekizumab, and brodalumab, are already in use for patients with rheumatologic conditions, including psoriasis and ankylosing spondylitis.[22]

HOW ARE IMMUNE-RELATED ADVERSE EVENTS TREATED?

Regardless of the precise mechanism, immune-related adverse events result from excessive immunity against normal organs. Thus, most immune-

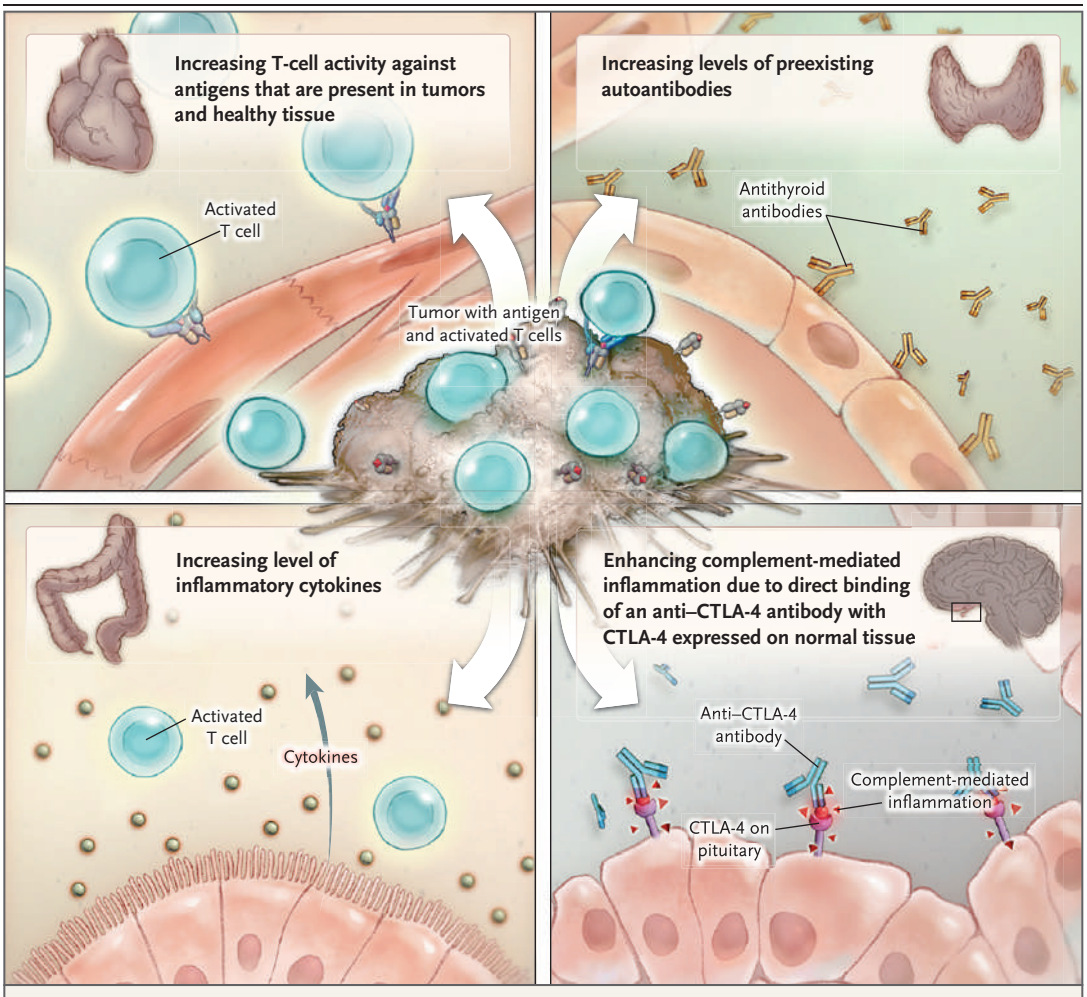

Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

related adverse events are effectively treated by delaying administration of the checkpoint inhibitor or by inducing temporary immunosuppression with agents such as oral glucocorticoids or additional immunosuppressants in more severe cases. Many reports describe algorithms based on clinical experience and provide detailed practical guidance for how to manage specific immune-related adverse events.[1,23-26]

Multidisciplinary collaboration can often be helpful in treating patients with immune-related adverse events. For example, infliximab, an antibody against tumor necrosis factor alpha that is used to manage Crohn's disease and ulcerative colitis, also has shown efficacy in patients with moderate-to-severe colitis induced by immune checkpoint blockade.[27] In treatment algorithms for immune-related adverse events, infliximab is usually recommended if glucocorticoids have not been successful. However, given the potential immediate efficacy of infliximab and the toxicity of long-term glucocorticoid therapy, an unanswered question is whether infliximab should be given earlier in the treatment of immune-related adverse events in order to minimize exposure to glucocorticoids. The experience with infliximab

raises the question of whether additional therapies for inflammatory bowel diseases, such as an anti–integrin $\alpha 4\beta 7$ antibody, vedolizumab, could be similarly effective for the treatment of colitis induced by immune checkpoint blockade, as suggested by a report on a case series.[28] Additional multidisciplinary cooperation among oncologists, other internal medicine specialists, and emergency medicine physicians may lead to the development of treatment strategies for rare, yet potentially life-threatening, immune-related adverse events, such as pneumonitis and myocarditis.[12,17]

WHEN DO IMMUNE-RELATED ADVERSE EVENTS OCCUR?

Immune-related adverse events usually develop within the first few weeks to months after treatment initiation. However, immune-related adverse events can present at any time, including after cessation of immune checkpoint blockade therapy, and may wax and wane over time. Several studies have indicated that with both anti–CTLA-4 and anti–PD-1 therapy, dermatologic toxicity occurs early.[1,29] Although anti–PD-1 or anti–PD-L1 therapy is occasionally given for months to years, most studies indicate that prolonged treatment does not result in an increased cumulative incidence of immune-related adverse events.[30] Nevertheless, whether immune checkpoint blockade creates later-term toxicity risk (i.e., many years after the initiation of therapy) is not known. This question will become an increasingly relevant as indications for this treatment expand to patients with cancer at earlier stages, when life expectancy may be measured in decades.

WHY DO THESE EVENTS OCCUR IN SOME PATIENTS BUT NOT OTHERS?

It is unclear why some patients have serious immune-related adverse events and others do not. Since genes influence the risk of certain autoimmune diseases in the absence of immune checkpoint blockade,[31-34] one line of investigation has examined whether underlying germline genetic factors are related to the likelihood of immune-related adverse events among patients treated with immune checkpoint blockade. In a pooled study involving 453 patients with melanoma who were treated with ipilimumab, no association was found between one specific genotype (HLA-A status) and the risk of immune-related adverse events.[35] However, much larger genomewide association studies may be needed to establish a relationship between genetic factors and the risk of immune-related adverse events.

In addition to genetic factors, some investigations have asked whether the microbiologic composition of a patient's gastrointestinal flora is related to the development of immune-related adverse events. Preclinical and emerging clinical data suggest that certain bacterial species are associated with the efficacy of immune checkpoint blockade,[36-38] which raises the possibility that variations in gastrointestinal flora that affect host immunity influence the risk. In two retrospective studies, the investigators concluded that patients with a predominance of bacteria from the Bacteroidetes phylum have reduced rates of ipilimumab-induced colitis.[39] How Bacteroidetes might influence this risk is unknown. Additional research is needed to determine whether manipulation of the microbiota through dietary intervention or use of probiotics or antibiotics could reduce the risk of colitis or other immune-related adverse events while maintaining the favorable antitumor effects of a particular gastrointestinal bacterial composition.

ARE THESE EVENTS ASSOCIATED WITH THE EFFICACY OF IMMUNE CHECKPOINT BLOCKADE?

Regardless of the precise pathophysiological mechanisms, the occurrence of immune-related adverse events provides evidence that immune checkpoint blockade has activated a patient's immune system. Whether this immunologic activation correlates with improved antitumor immunity remains controversial. The repertoire of antigen specificities is quite large, and the hope is that with nonspecific activation of the immune system, some of the cells may recognize and kill the tumor; however, the vast majority of activated cells do not. Does the magnitude of immune activation increase the chances of success? Is the severity of immune-related adverse events a measure of the likelihood of an antitumor response? Some studies suggest that patients with immune-related adverse events have higher response rates than patients without such events, but these findings have not been universally veri-

fied.[1,40,41] In one large, retrospective study of ipilimumab, the treatment outcomes were similar in patients with and those without immune-related adverse events.[42] At minimum, the general consensus is that such events are not required to obtain a benefit from immune checkpoint blockade.

It is possible that certain immune-related adverse events are more directly related to antitumor efficacy than others. For example, several studies involving patients with melanoma have shown an association between vitiligo and beneficial clinical outcomes.[43,44] It has been known since at least 1964 that vitiligo can develop in patients undergoing immune stimulation for the treatment of melanoma.[45] Vitiligo is not a common side effect in patients with other cancers who receive treatment with immune checkpoint blockade, which suggests that immune-related adverse events may vary according to the tumor type. However, it is clear that the toxic effects that occur in patients with different tumor types can be very similar, a finding that leads to the notion that the manifestations are more closely related to the immune system than to the tumor. Immune-related adverse events that are directly related to antigen-specific immunity, such as vitiligo, may be more strongly correlated with antitumor efficacy than other immune-related adverse events.

DOES IMMUNOSUPPRESSION REDUCE THE ANTITUMOR EFFICACY OF IMMUNE CHECKPOINT BLOCKADE?

Since immune checkpoint blockade works by increasing antitumor immunity, clinicians have wondered whether systemic immunosuppression that is used to treat immune-related adverse events may interfere with the therapeutic efficacy of immune checkpoint blockade. No formal, prospective studies testing immunosuppressive strategies have been conducted to answer this question. Nonetheless, retrospective studies have shown that the outcomes for patients whose immune-related adverse events were treated with immunosuppression were not worse overall than the outcomes for patients who did not receive immunosuppressive agents for immune-related adverse events,[1,42] though there may be individual exceptions, perhaps relating specifically to the type of immunosuppressive treatment used.[21] Studies exploring potential relationships between various aspects of immunosuppression — type, timing, and duration — and clinical outcomes are needed.

DOES IMMUNOSUPPRESSION HAVE UNINTENDED EFFECTS?

Although the theoretical risk that immunosuppression reduces antitumor efficacy has not been proved, immunosuppression does carry additional risks that clinicians should consider. Specifically, the use of glucocorticoids can result in hyperglycemia, fluid retention, and anxiety, as well as iatrogenic adrenal insufficiency if the glucocorticoids are tapered too quickly. Although longer-term glucocorticoid therapy is infrequently needed to treat immune-related adverse events, such treatment can lead to additional complications, such as cushingoid features, osteoporosis, glaucoma, opportunistic infections, and debilitating proximal muscle weakness.[46,47]

In addition, immunosuppression for the treatment of immune-related adverse events may place patients at risk for opportunistic infections such as *Aspergillus fumigatus* pneumonia,[48] cytomegalovirus hepatitis, and pneumocystis pneumonia.[49,50] In a retrospective study involving 790 patients with advanced melanoma who were treated with immune checkpoint blockade, the rate of serious infections was 13.5% in the subgroup of patients who received either glucocorticoids or infliximab for the management of immune-related adverse events.[51] Given this potential risk of opportunistic infection, when patients require 20 mg of prednisone daily or the equivalent for at least 4 weeks, *Pneumocystis jirovecii* prophylaxis with trimethoprim–sulfamethoxazole, atovaquone, or pentamidine should be considered.[52]

IS IT SAFE TO RESTART IMMUNE CHECKPOINT BLOCKADE AFTER A SERIOUS ADVERSE EVENT?

Since most immune-related adverse events resolve within weeks to months after the initiation of immunosuppressive therapy,[1] one of the most important issues in clinical practice is the safety of resuming immune checkpoint blockade after the adverse event has resolved. Prospective data from clinical trials are limited, since study protocols have often required that treatment with

immune checkpoint blockade be permanently discontinued if a serious immune-related adverse event develops. A recent retrospective study involving patients with melanoma showed that anti–PD-1 therapy could be safely given after a serious ipilimumab-related adverse event requiring immunosuppression.[53] Subsequent anti–PD-1 treatment was associated with a low rate of recurrent immune-related adverse events (3%). These findings suggest that toxicity may be treatment-specific rather than generalizable across the various types of immune checkpoint blockade, which have nonredundant biologic effects.

More specific to the question of the safety of restarting therapy, another retrospective study described patients with non–small-cell lung cancer (NSCLC) treated with anti–PD-1 or anti–PD-L1 therapy who had immune-related adverse events requiring a delay in treatment, treatment with glucocorticoids, or both and who were later retreated with anti–PD-1 or anti–PD-L1 therapy.[54] Among 38 patients who were retreated, 50% had no further immune-related adverse events, 24% had a recurrence of the initial event, and 26% had a new event. Thus, clinicians should recognize that restarting immune checkpoint blockade after the resolution of immune-related adverse events may trigger recurrent or new immune-related adverse events. Although recurrent adverse events are usually less severe than the initial events (probably because of heightened surveillance), a decision to restart treatment with immune checkpoint blockade is likely to depend on the severity of the prior event, the availability of alternative treatment options, and the overall status of the cancer. An absolute contraindication to restarting treatment with immune checkpoint blockade is life-threatening toxicity, particularly cardiac, pulmonary, or neurologic toxicity.

IS IT NECESSARY TO RESTART IMMUNE CHECKPOINT BLOCKADE AFTER EVENT RESOLUTION?

Even if we can sometimes restart treatment after an immune-related adverse event, a separate question is whether we should do so. Again, on this point data remain limited. In a study involving patients with advanced melanoma who were treated with a combination of nivolumab and ipilimumab, those who discontinued the treatment because of toxicity during the first 4 months had rates of progression-free and overall survival that were similar to the rates for patients who continued therapy longer.[55] In a series of patients with NSCLC who had a favorable response to treatment with immune checkpoint blockade and then had an immune-related adverse event that resulted in treatment discontinuation or delay, rates of progression-free and overall survival among the patients who restarted treatment after resolution of the adverse event were equivalent to the rates among those who permanently discontinued treatment.[54] Additional follow-up of patients in these retrospective studies and additional prospective studies are needed to confirm that the extent of the benefit is not affected by a shorter duration of immunotherapy.

IS IT SAFE TO TREAT PATIENTS AT INCREASED RISK FOR SUCH EVENTS?

It is possible that some patients are at increased risk for immune-related adverse events, such as patients with underlying autoimmune disease, organ or hematopoietic stem-cell transplants, chronic viral infection, organ dysfunction, or advanced age. Most of the evidence regarding immune-related adverse events comes from prospective clinical trials, but several patient populations, such as those with autoimmune diseases, were not included in clinical trials, so the safety of immune checkpoint blockade is less clear for these patients.[56] Several retrospective studies nonetheless suggest that patients with underlying autoimmune disorders can be treated safely and effectively with immune checkpoint blockade.[53,57] Although such patients may be at increased risk for transient exacerbation of their autoimmune condition and for immune-related adverse events in general, these events have generally not been high-grade toxic effects. It is our opinion that patients with an underlying autoimmune disorder should be considered for treatment with immune checkpoint blockade if they have a life-threatening cancer and that the risks and benefits of such therapy should be weighed in consultation with appropriate subspecialists.

The safety of immune checkpoint blockade in recipients of solid-organ transplants is also uncertain. More cases of graft rejection have been reported with anti–PD-1 or anti–PD-L1 therapy than with ipilimumab therapy.[58-61] Since more patients receive anti–PD-1 or anti–PD-L1 therapy,

the greater frequency of published reports of transplant rejection may not necessarily mean that the risk of rejection is higher with anti–PD-1 or anti–PD-L1 agents than with ipilimumab. The consequences of graft rejection also need to be considered. Renal failure due to renal-allograft rejection could be managed with hemodialysis; management of cardiac failure from cardiac-transplant rejection, although possible,[61] may be more difficult. Immune checkpoint blockade should be used cautiously in this patient population when other similarly effective treatment options are not available and should be monitored in close collaboration with transplant specialists.

The safety of immune checkpoint blockade after allogeneic hematopoietic stem-cell transplantation is being explored.[62] In a study involving 28 patients treated with ipilimumab, 21% of the patients had immune-related adverse events, with one treatment-related death due to colitis and pneumonitis. Liver and gastrointestinal graft-versus-host-disease (GVHD) was also reported. It remains unclear whether this is evidence of an increased risk of immune-related adverse events or GVHD. Additional studies of anti–PD-1 or anti–PD-L1 treatment after allogeneic transplantation are needed, especially in view of emerging evidence of the efficacy of anti–PD-1 agents in patients with hematologic cancers.[63-65]

Patients with chronic viral hepatitis or human immunodeficiency virus (HIV) infection have also been excluded from trials of treatment with immune checkpoint blockade in most cases. However, one prospective study of nivolumab in patients with hepatocellular carcinoma showed that side effects in patients with hepatitis B or hepatitis C were similar to the side effects in patients without viral hepatitis.[66] Less is known about the safety of immune checkpoint blockade in patients with HIV infection, but several case reports have shown that such therapy can be safely given to patients with melanoma or NSCLC who also have HIV infection.[67-69] Overall, treatment with immune checkpoint blockade in patients with chronic viral infections appears to be safe, but the importance of multidisciplinary collaboration cannot be overemphasized.

There are minimal data on the safety of immune checkpoint blockade in patients with renal or hepatic insufficiency. Nonetheless, since the agents that are used for immune checkpoint blockade are antibodies that are not cleared by the kidneys or liver, the efficacy and safety of these agents in patients with renal or hepatic impairment should be similar to their efficacy and safety in patients without such impairment. A prospective study of atezolizumab in patients with advanced urothelial carcinoma included patients with renal impairment (glomerular filtration rate, >30 but <60 ml per minute).[70] Atezolizumab was effective (25% objective response rate), but the rate of immune-related adverse events was not reported. In a separate, retrospective analysis, three patients who were undergoing hemodialysis were treated with immune checkpoint blockade, and none had immune-related adverse events.[71] Even less is known about the safety of immune checkpoint blockade in the context of hepatic impairment, but some patients with radiographic evidence of cirrhosis or abnormal liver-function tests have been treated without an obvious increase in toxicity.[66] Given the possibility of a treatment benefit and no demonstrated increase in risk, patients with renal or hepatic impairment can be candidates for treatment with immune checkpoint blockade.

Older adults are also underrepresented in clinical trials. However, subgroup analyses from prospective trials and retrospective studies suggest that the efficacy of immune checkpoint blockade in older adults is similar to the efficacy in younger adults, without an increase in immune-related adverse events.[72] Similarly, a meta-analysis showed that the benefit from treatment with immune checkpoint blockade in randomized studies did not appear to be dependent on age.[73] Even carefully selected patients older than 90 years of age have been safely and effectively treated with immune checkpoint blockade.[74] Thus, age itself should not be factored into decisions about whether to use this treatment approach. Comprehensive geriatric assessment and measures of frailty may be important predictors of immune-related adverse events and a decreased quality of life, but this possibility requires additional research.

CONCLUSIONS

Immune checkpoint blockade is an increasingly important cancer treatment. Several studies have shown that it has a better safety profile than chemotherapy.[75,76] Nevertheless, immune-related

adverse events requiring specialized management can ensue. Most of the toxic effects are reversible, aside from effects on the endocrine system, which may be permanent. Fortunately, deaths from immune-related adverse events are exceptionally rare, but deaths due to myocarditis, pneumonitis, colitis, and neurologic events, among others, can occur.

There are at least three important opportunities to improve the treatment of immune-related adverse events and refine answers to the 10 questions addressed in this review. First, studies are needed to elucidate mechanisms of immune-related adverse events (i.e., events mediated by antibodies, T cells, and cytokines) in order to develop more precise treatments for immune-related adverse events. Second, establishing international registries may be helpful in capturing real-world data regarding immune-related adverse events in patient populations that are underrepresented in clinical trials. Finally, as clinical experience with these agents increases, multidisciplinary clinical involvement will be needed to share insights from various fields of medicine to realize the full potential of this treatment approach.

Dr. Postow reports receiving grant support, paid to his institution, and consulting fees from Bristol-Myers Squibb, honoraria from Merck and Bristol-Myers Squibb, and consulting fees and advisory board fees from Novartis, Ono Pharmaceutical, Array BioPharma, Merck, Incyte, and NewLink Genetics; and Dr. Hellmann, receiving consulting fees and advisory board fees from Genentech, Merck, AstraZeneca, Novartis, Janssen, and Mirati Therapeutics and grant support, consulting fees, and advisory board fees from Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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