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# Balancing Cancer Immunotherapy Efficacy and Toxicity



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**Anti-programmed cell death-1 receptor/programmed cell death-1 receptor ligand-directed therapies are transforming cancer care, with durable antitumor responses observed in multiple cancer types. Toxicities arising from therapy are autoimmune in nature and may affect essentially any organ system. The immunologic basis of such toxicities is complex, with contributions from T-cell activation and autoantibody generation. Although less recognized, hypersensitivity reactions are also possible. Although most toxicities resolve with systemic corticosteroids, some require second-line immunosuppression. Furthermore, the safety of drug rechallenge is not well characterized, with variable rates of toxicity flares arising with re-exposure. Herein, we review toxicities of immune checkpoint inhibitor therapies, particularly focusing on issues that allergists/immunologists may clinically encounter, including interstitial nephritis, skin toxicity, and risks associated with immunotherapy rechallenge.** © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:2898-906)

**Key words:** Anti-PD-1; Anti-PD-L1; Allergy; Immune-related adverse event; Rechallenge; Nephritis; Dermatitis

## INTRODUCTION

A 67-year-old man with metastatic non-small cell lung cancer, hypertension, and gastroesophageal reflux presents to your clinic for evaluation of possible drug hypersensitivity. He has been receiving pembrolizumab 2 mg/kg intravenously every 3 weeks for the past 15 months and has had a partial response to therapy, with decreased tumor burden by approximately 50%. For the first year on therapy, his only complaint had been an intermittent grade 1 maculopapular eruption on his arms and trunk (<10% of body surface area affected), which had been managed with topical triamcinolone and occasional cetirizine 10 mg daily. Approximately 1 month before presentation, he developed worsening of his kidney function on routine laboratory

evaluation, with increased creatinine level to a peak of 3.5 mg/dL (baseline, 1.1 mg/dL). His other long-standing medications included omeprazole and hydrochlorothiazide. He reported no decreased oral intake, and did not have recent exposure to intravenous contrast nor any over-the-counter medications. No other symptoms were detected on review of systems. His blood cell counts were normal, including a normal leukocyte differential. Urinalysis showed trace proteinuria, no erythrocytes, and 3 to 5 leukocytes without cellular casts noted on urine microscopy. Renal ultrasound was unremarkable. Pembrolizumab was withheld, and the patient was treated with prednisone 1 mg/kg with normalization of his creatinine over the next week. Prednisone was tapered over the subsequent 4 weeks and he is now taking prednisone 10 mg daily with plans to discontinue in 3 days. The patient asks whether he can receive more pembrolizumab.

## OVERVIEW: IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors (ICIs) are mAbs that remove key negative regulators of T-cell function. These agents are approved in 17 different cancer types, and have radically transformed oncology treatment paradigms.<sup>1</sup> Approved agents include pembrolizumab, nivolumab, and cemiplimab, which target the programmed cell death-1 receptor (PD-1); atezolizumab, avelumab, and durvalumab, which target the programmed cell death-1 receptor ligand (PD-L1); and ipilimumab, which targets cytotoxic T-lymphocyte antigen-4 (CTLA-4). Response rates for anti-PD-1/PD-L1 vary widely from 80% to 90% (for Hodgkin lymphoma) to 45% to 60% (for skin cancers and microsatellite unstable cancers) to 15% to 30% (for many other solid tumors including cancers of the lung, kidney, bladder, and head and neck).<sup>2</sup> In contrast, anti-CTLA-4 has a lower degree of activity as a single agent, with approximately a 20% response rate in melanoma, and little activity in other malignancies (albeit with fairly sparse data).<sup>3</sup> The combination of PD-1 and CTLA-4 inhibitors produces improved outcomes in several cancer types. For example, this combination is associated with an approximately

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D.B.J. is funded by the National Institutes of Health/National Cancer Institute (grant nos. K23 CA204726 and R01CA227481).

Conflicts of interest: D. B. Johnson serves on advisory boards for Array Biopharma, Bristol Myers Squibb, Merck, and Novartis, and receives research funding from BMS and Incyte. V. Sibaud has served on advisory boards for Incyte, Pierre Fabre,

BMS, Bayer, and Novartis. M. E. Sise has been an investigator on research grants awarded to Massachusetts General Hospital from Merck, Abbvie, Gilead, and EMD-Serono, and has served as a scientific advisory board member for Gilead, Abbvie, and Merck. B. D. Jakubovic has no relevant conflicts of interest.

Received for publication April 22, 2020; revised manuscript received and accepted for publication June 9, 2020.

Available online June 26, 2020.

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<https://doi.org/10.1016/j.jaip.2020.06.028>

*Abbreviations used*

*AIN*- acute interstitial nephritis  
*AKI*- acute kidney injury  
*CTCAE*- Clinical Trial Criteria for Adverse Events  
*CTLA-4*- cytotoxic T-lymphocyte antigen-4  
*ICI*- immune checkpoint inhibitor  
*irAE*- immune-related adverse event  
*PD-1*- programmed cell death-1 receptor  
*PD-L1*- programmed cell death-1 receptor ligand

60% response rate in metastatic melanoma, compared with approximately 45% for single agent anti-PD-1.<sup>4</sup> Importantly, many responses are extremely durable (perhaps even lasting for decades), leading to extended benefit in previously treatment-refractory settings.<sup>5,6</sup>

The mechanisms of action of ICIs are quite distinct from most conventional cancer therapies. ICIs fall within a broader category of immunotherapy approaches that highlight the revolutionary shift toward precision-based cancer treatment. Instead of directly targeting cancer cells, ICIs largely bind to molecules on immune cells and augment the body's immune defenses to eradicate neoplastic cells.<sup>7</sup> During immune priming, antigen-presenting cells engage with T cells, and require a second signal for T-cell activation in addition to the T-cell receptor/MHC interaction (Figure 1). The major second signal is B7 (on antigen-presenting cells) engaging CD28 (on T cells). Because CTLA-4 opposes this interaction, blocking CTLA-4 (as with ipilimumab) allows for enhanced T-cell activation. In sites of inflammation or in the tumor microenvironment, cells often upregulate PD-L1 in response to IFN- $\gamma$ , or may constitutively express PD-L1. PD-1, which is expressed on T cells, engages with PD-L1 to repress T-cell effector function and produce a state of T-cell "exhaustion." Blocking either PD-1 or PD-L1 allows for reinvigoration of T-cell function and tumor cell cytotoxicity. Although there are slight differences in the mechanism of action between these drugs (PD-1 binds PD-L1 and PD-L2, whereas PD-L1 binds PD-1 and B7-1), inhibition of either PD-1 or PD-L1 produces largely similar clinical outcomes.

**OVERVIEW: ICI TOXICITIES**

The power of blocking these key immune regulators and unleashing antitumor T-cell responses is most evident in the improved survival even in cancers for which standard therapies were associated with abysmal outcomes (ie, stage 4 melanoma). However, the drawback of this strategy is that widespread T-cell disinhibition may generate autoreactive T cells capable of targeting self-antigens and host tissues. These aberrant responses produce autoimmune-like adverse events that may involve essentially any organ system, although most often involve the skin, thyroid, colon, and lungs.<sup>8</sup> Toxicities may occur any time while on therapy (even up to 6 months after discontinuing treatment), but peak between 1 and 12 weeks after starting. Hence, drug-induced immune-related adverse events (irAEs) should be considered in the differential diagnosis in all patients exposed to ICIs. Severe immune-related toxicities occur in approximately 20% of patients on anti-PD-1 (likely slightly lower rates with anti-PD-L1), and 40% to 50% of patients treated with combined PD-1/CTLA-4 blockade.<sup>9</sup> Similarly, mild irAEs occur in nearly all patients treated with combination

therapy compared with 60% to 70% of patients on anti-PD-1/PD-L1 monotherapy.

Technical classification of these events is based on the Clinical Trial Criteria for Adverse Events (CTCAE), an imperfect tool designed to standardize classifications of adverse events on clinical trials.<sup>10</sup> For the purposes of this review, they may be categorized by severity (mild, moderate, severe) and by response to treatment (responsive vs refractory). Mild toxicities (CTCAE grade 1) are managed with symptomatic management (eg, moderate- to high-potency topical corticosteroids for pruritic rash) and continuation of ICIs, whereas treatment may be held for moderate events (CTCAE grade 2). For persistent moderate, severe, or life-threatening events (CTCAE grades 2-4), patients should hold ICIs and receive prednisone 1 to 2 mg/kg or equivalent and supportive management. The persistent pharmacokinetic and pharmacodynamic properties (lasting weeks to months) of ICIs require that severe events be treated with steroids and potentially other immunomodulators rather than simply drug cessation alone. Steroid-refractory events may be treated by disease-specific immunosuppressants (eg, infliximab for colitis and mycophenolate mofetil for hepatitis). Although typically manageable with standard treatment algorithms, some toxicities become chronic and occasionally even fatal (in 1.2% of patients treated with combination PD-1/CTLA-4 blockade).<sup>11</sup> In aggregate, steroid-refractory toxicities (defined as those needing steroid re-escalation, second-line immunosuppression, or causing death) occurred in 23% of patients receiving combination therapy and only 3% of those on anti-PD-1 monotherapy in one series.<sup>12</sup> Of note, because very little high-level evidence exists for the management of ICI toxicities, most recommendations are based on expert opinion, retrospective series, and anecdotal evidence rather than randomized prospective clinical trials.<sup>13,14</sup>

Monitoring for these irAEs is a critical component of management. Most providers obtain complete blood cell count and complete metabolic profile at each cycle to monitor bone marrow, kidney, and liver function. Thyroid function tests should be obtained at least every other treatment. We obtain cortisol and troponin measurements to assess for cardiac and adrenal dysfunction specifically for patients on combination PD-1/CTLA-4 blockade. In addition, oxygen saturation may help diagnose pneumonitis. Otherwise, close symptom checks and skin examinations at every visit are performed, with particular attention paid to the gastrointestinal, pulmonary, and dermatologic systems.

Although the general mechanisms of these events are well known (ie, removal of immune checkpoints, which results in T-cell activation), the reasons why certain patients experience organ-specific events or multisystem involvement remain unclear. Proposed mechanisms of toxicity include T-cell targeting of shared antigens common to both tumor and inflamed tissue,<sup>15,16</sup> preexisting autoantibodies,<sup>17,18</sup> and microbial factors (specifically cross-reactive memory T-cell response to a pathogen to which the host has previously been infected) inducing inflammation that is further exacerbated by ICI therapy.<sup>19,20</sup> Direct T-cell targeting of organ tissue, as well as autoantibody generation, may occur with toxicities.<sup>9</sup> As such, these events are distinct from classical drug hypersensitivity. We will briefly review specific toxicities (Table I), with more extensive sections on events that may be more relevant to allergists: skin toxicities and interstitial nephritis.

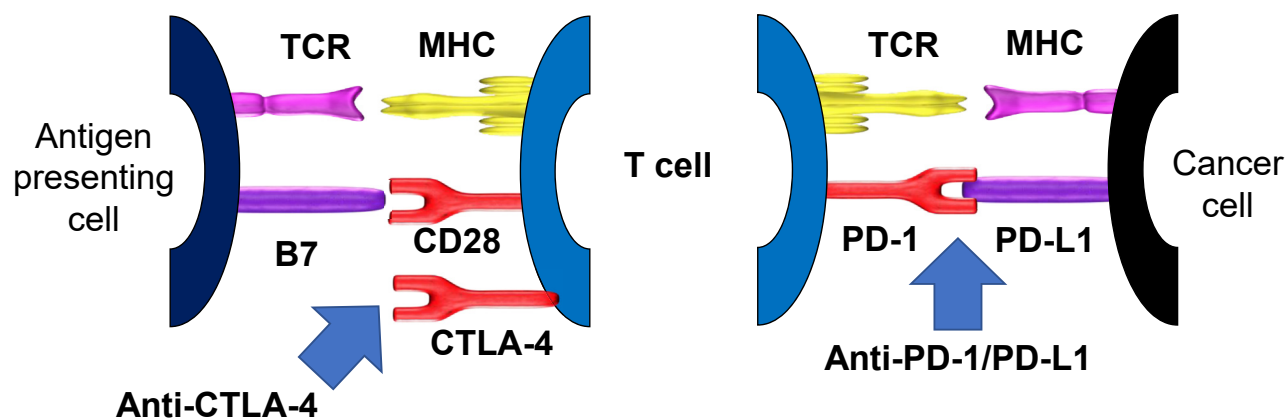


FIGURE 1. Mechanism of action of anti-PD-1/PD-L1 and anti-CTLA-4 therapies.

### Dermatologic toxicities

Dermatologic adverse events are among the most frequent toxicities reported with ICIs.<sup>21</sup> They affect about one-third of the patients treated with anti-PD-1.<sup>21,22</sup> The overall incidence is slightly higher with anti-CTLA-4 antibodies.<sup>3</sup> Moreover, dermatologic toxicities are significantly more frequent and more severe and develop earlier with anti-CTLA-4/anti-PD-1 therapies used in combination.<sup>23</sup>

Although pathogenesis remains to be elucidated, the most frequent skin toxicities (eg, eczema-like or lichenoid rashes) are likely related to the triggering of a cytotoxic CD4<sup>+</sup>/CD8<sup>+</sup> activation against dermal-epidermal self-antigens not yet determined. These antigens may be shared between tumor and healthy skin tissue, with the same infiltrating T-cell clonotypes in both sites as individualized by Berner et al.<sup>15</sup> However, the involvement of humoral immunity has been also recently suggested, notably through the production of IgG antibodies against several shared antigens, such as the hemidesmosomal component BP 180.<sup>24</sup>

The development of a pruritic maculopapular eruption with flat-topped, erythematous, and scaly lesions represents the most common cutaneous irAE. It affects about 15% of patients treated with anti-PD-1 therapies. Lesions usually arise within the first few weeks of treatment. They predominate on the trunk but can more widely extend to the whole body, with a relative sparing of the face. However, in the vast majority of cases, lesions remain self-limited, with a low rate of grade 3 or higher.<sup>21,25</sup> In our experience, the most common histopathologic features are nonspecific eczematous spongiotic changes.<sup>21,22,26</sup> However, more characteristic aspects can also be individualized and a skin biopsy should be systemically performed in the case of atypical, persistent, recurrent, or intolerable grade 2 or grade 3 rash. Lichenoid reactions with a vacuolar interface dermatitis are also common. They can involve the skin, the nails, and the genital or oral mucosa.<sup>25,27</sup> The overall risk of developing psoriasis with ICIs is also well established.<sup>26,28</sup> In most cases, patients have a familial or personal history of psoriasis. Multiple subtypes can be seen, including plaques psoriasis, guttate lesions, pustules, and palmoplantar or inverse psoriasis. Vitiligo-like depigmentation represents a frequent toxicity of anti-PD-1.<sup>22,29</sup> It roughly affects 8% of patients with advanced melanoma treated with agents targeting PD-1. In contrast, it has been exceptionally described in patients treated for other types of cancer. See Figure 2 for examples of the diverse presentations of ICI-skin toxicities.

ICIs can also be associated with the development or the worsening of granulomatous sarcoid-like dermatitis and autoimmune skin disorders. The most common type is bullous pemphigoid, which can appear in 1% of treated patients.<sup>30</sup> Direct immunofluorescence and analysis by ELISA (detection of BP180 antibodies) are required for diagnosis. Subacute lupus erythematosus, Sicca syndrome and Sjogren syndrome, autoimmune vasculitis, or dermatomyositis have been also reported.<sup>31</sup>

Pruritus may also occur without rash, and may produce similar morbidity compared with pruritus associated with an eruption.<sup>32</sup> This entity appears to have distinct pathophysiology. ICI-mediated eruptions seem to stem from immune-mediated targeting of cells in the epidermis or dermis, whereas pruritus without rash appears to have a neurogenic component.<sup>26</sup> Gabapentin and other GABA-ergic agents appear more efficacious than steroids in these patients.<sup>33</sup>

In most cases, skin toxicities remain reversible, readily manageable, and do not require treatment interruption or withholding. However, they may result in significant morbidity, with a negative impact on patient quality of life. Conservative management with skin-directed therapy, including moderate- to high-potency corticosteroids and moisturizers, represents the first line of treatment.<sup>21,26</sup> However, a subset of patients may require specific systemic treatments and the therapeutic decision must then be discussed in a multidisciplinary framework. These may include omalizumab or rituximab (bullous pemphigoid), narrowband ultraviolet therapy, anti-TNF agents, methotrexate, acitretin or apremilast (psoriasis), systemic corticosteroids or retinoids (lichenoid reactions), or, as recently suggested, biologic immunomodulatory therapies including with mAbs targeting IL-4 (dupilumab) or IL-6 (tocilizumab) for severe or persistent rashes.<sup>26,34</sup> Finally, the occurrence of most dermatological toxicities (with the possible exception of pruritus without rash) can be considered as a positive prognostic factor and appears to be correlated with a better progression-free or overall survival.<sup>22,35</sup>

### Renal toxicities

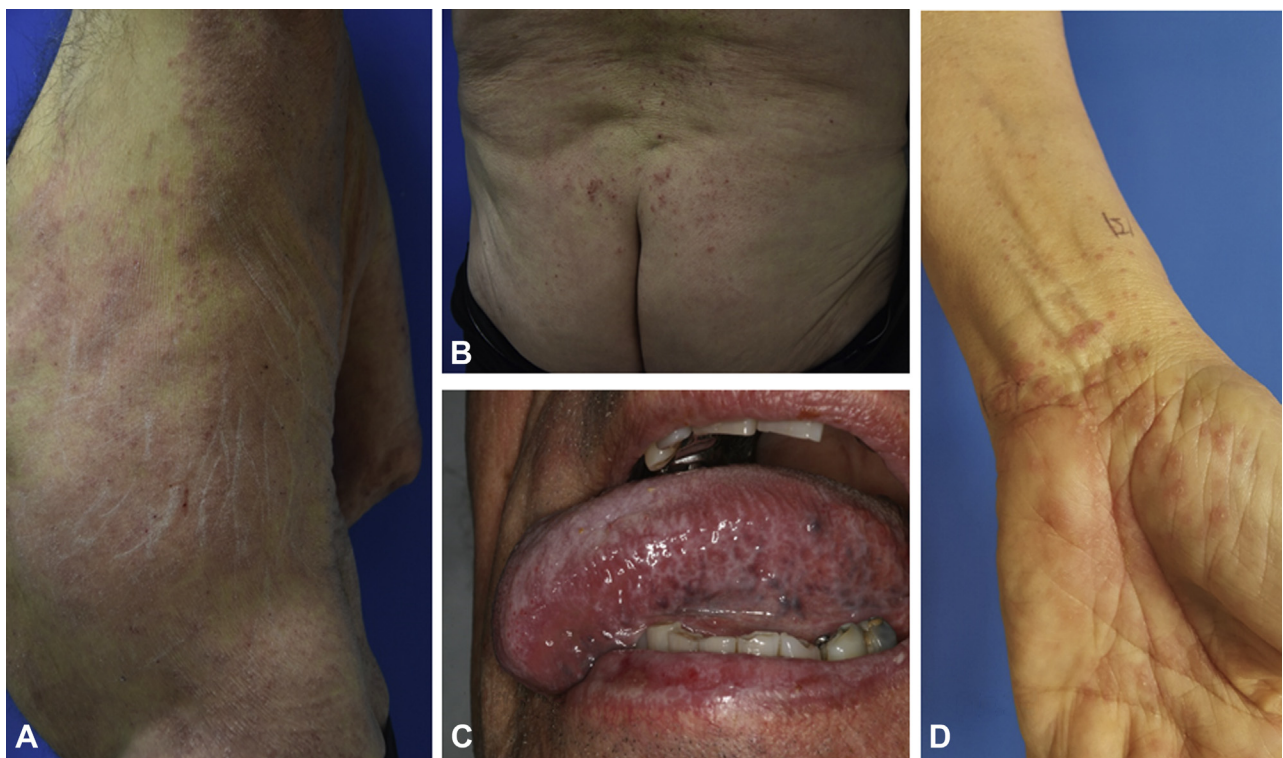
Immune-mediated kidney disease is a rare complication of ICI therapy. In 2016, Cortazar et al<sup>36</sup> described 13 cases of ICI-induced acute kidney injury (AKI) across 7 medical centers who underwent kidney biopsy. Acute interstitial nephritis (AIN) was the primary lesion in 12 of 13 cases (the final case had thrombotic microangiopathy). An 18-center study that included

**TABLE 1.** ICI toxicities, presentation, and therapy

Toxicity	Clinical presentation	Diagnostic approach	First-line therapy*	Second-line therapy
Dermatitis	Various eruptions	Clinical examination, skin biopsy	Topical steroids, oral steroids	Anti-TNF, omalizumab, acitretine, methotrexate, dupilumab, rituximab, UV therapy
Endocrinopathy	Fatigue, hypotension, metabolic changes	TSH, T4, cortisol, ACTH	Hormone replacement	
Colitis	Diarrhea, abdominal pain	Clinical, endoscopy	Oral steroids	Infliximab, vedolizumab
Pneumonitis	Cough, shortness of breath	Chest CT, clinical	Oral steroids	Infliximab, IVIG
Hepatitis	Usually asymptomatic	AST, ALT	Oral steroids	MMF
Nephritis	Usually asymptomatic	Creatinine, urinalysis and microscopy, renal biopsy	Oral steroids	MMF, rituximab, infliximab
Myocarditis	Shortness of breath, chest pain	Troponin, myocardial biopsy, cardiac MRI	Oral steroids	Abatacept, alemtuzumab, MMF, IVIG
Neurotoxicity	As with encephalitis, Guillain-Barre syndrome, myasthenia gravis	Neuroimaging, clinical examination, lumbar puncture	Oral steroids	IVIG, plasma-pheresis, rituximab

ACTH, Adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone; UV, ultraviolet.

\*First-line therapy presumes persistent grade 2 or grade 3-4 except in dermatitis; also involves holding the ICI treatment except with endocrinopathies.



**FIGURE 2.** (A) Grade 3 pruritic eczema-like rash with apparent scratches. (B) Limited eczematous eruption. (C) Oral lichenoid reaction on the lateral aspect of the tongue, with reticular streaks. (D) Typical lichenoid skin lesions.

138 cases of ICI-AKI showed that AIN was found in 93% of those who underwent biopsy.<sup>36</sup> More than half of all cases of ICI-AIN co-occur with other extrarenal irAEs.<sup>36,37</sup> ICI-AIN is clinically characterized by a rise in serum creatinine level without associated heavy proteinuria. ICI-AIN is rarely associated with rash or eosinophilia, and leukocyturia occurs in only half. Urine eosinophils are not useful in the diagnosis of AIN either.<sup>38</sup>

Imaging studies, such as gallium scanning or positron emission tomography, have shown potential promise in diagnosing AIN, but are not commonly used for this indication.<sup>39,40</sup> Thus, because there are no consistent blood, urine, or imaging findings that can confirm the diagnosis of ICI-AIN, either clinical diagnosis or renal biopsy would be required. Pathologically, ICI-AIN is indistinguishable from other forms of drug-induced AIN, with

typical biopsy findings demonstrating dense interstitial inflammatory infiltrate of leukocytes including lymphocytes, neutrophils, and eosinophils, as well as tubulitis. Severe tubulitis can lead to tubular basement membrane rupture and interstitial granuloma formation. Multiple studies have noted that a large number of patients with ICI-AIN are on other medications associated with AIN at the time that AKI develops, such as proton pump inhibitors, antibiotics, or nonsteroidal anti-inflammatory drugs.<sup>36,37,41-43</sup> A large cohort study noted that on a population level, proton pump inhibitor use increased the risk of developing sustained AKI after ICI initiation.<sup>37</sup> Blocking PD-1/PD-L1 and CTLA-4 pathways may inadvertently lead to activation of T cells to drug antigens, driving hypersensitivity of the skin and kidney.<sup>44</sup> Further study into the mechanism of ICI-AIN is needed.

It is important to note that a small number of patients develop immune-related glomerular diseases after ICIs with a wide variety of other pathologies found on kidney biopsy, including lupus nephritis, vasculitis, or podocytopathies.<sup>45</sup> Because each of these entities may require different treatment strategies, this highlights the importance of kidney biopsy to determine the etiology of AKI in patients on ICI therapy with unexplained AKI or new-onset proteinuria.

Fortunately, ICI-AIN commonly responds favorably and quickly to corticosteroids. Guidelines recommend holding ICIs and evaluating any patient whose serum creatinine level rises 1.5-fold above baseline (ie,  $\geq$ stage 1 AKI), and an empiric course of steroids 0.5 to 1 mg/kg/d is recommended for a patient with stage 2 AKI ( $\geq$ 2-fold rise in serum creatinine level) when alternative causes are excluded.<sup>13</sup> We also recommend discontinuation of any other medication associated with AIN (such as nonsteroidal anti-inflammatory drugs or proton pump inhibitors). In a multicenter retrospective study, 85% of patients responded to corticosteroids with either partial or full remission regardless of dose/duration used and less than 10% needed a second-line immunosuppressant.<sup>36</sup> The optimal immunosuppressive treatment for patients who develop immune-mediated glomerular diseases after ICIs is unknown.

### Colitis

Colitis is one of the more common, potentially life-threatening complications of ICI therapy, arising in up to 20% of combination treated patients (but only <5% of anti-PD-1/PD-L1 monotherapy).<sup>46</sup> Presenting most often with diarrhea (~90%) rather than hematochezia (<10%) or abdominal pain, colitis is usually diagnosed clinically. Endoscopic confirmation with visual inspection and biopsy may provide confirmation if there is diagnostic uncertainty, and may also provide additional clinical information. For example, ulcerations seem to be correlated with steroid-refractory disease,<sup>47</sup> and occasionally microscopic colitis may be diagnosed, which can respond to budesonide rather than high-dose steroids.<sup>48</sup> Still, in most unequivocal cases, high-dose steroids may be used empirically, with escalation to infliximab if no improvement is observed within 3 days. Untreated or extremely severe cases may result in intestinal perforation.

### Pneumonitis

ICI-pneumonitis occurs more commonly with anti-PD-1 and combination therapies (ranging from 3% to 10% in some series) than with anti-CTLA-4, and occurs more often in

patients with lung cancer than in patients with melanoma.<sup>49</sup> Of note, there is no evidence that patients with asthma experience exacerbation of their asthma symptoms while on ICIs, although systematic data collection has not been performed, and preclinical evidence suggests they could worsen allergic asthma.<sup>50</sup> Clinically, this entity usually presents with dry cough, which may be accompanied by shortness of breath; fever and productive cough are much less common. Radiographically, 5 distinct and diverse patterns have been reported (groundglass opacities, cryptogenic-organizing pneumonia-like, interstitial, hypersensitivity, and not otherwise specified).<sup>51</sup> Patients with lung cancer have a particularly high incidence of pneumonitis; these patients also have a high incidence of other causes of respiratory compromise including infection and progression of neoplastic disease. Thus, a high index of suspicion is particularly needed in these patients. In steroid-refractory cases, mycophenolate mofetil, intravenous immunoglobulin, or infliximab may be used. Although most patients recover, pneumonitis may result in the most total numbers of deaths from ICI toxicity.<sup>11</sup>

### Hepatitis

Hepatic inflammation associated with ICIs tends to be diagnosed with laboratory values in asymptomatic patients. Typically, aspartate transaminase and alanine aminotransferase are elevated rather than alkaline phosphatase or bilirubin (although the latter may rise in severe or prolonged cases).<sup>52</sup> Ultrasound, viral hepatitis serologies, and acetaminophen levels may be helpful to rule out alternative causes. Steroid-refractory cases frequently respond to mycophenolate mofetil. Fulminant liver failure, while very uncommon, may respond to antithymocyte globulin or intravenous immunoglobulin.<sup>53</sup>

### Endocrine toxicities

Thyroid abnormalities are among the most common events affecting patients treated with ICIs, affecting up to 20% of patients treated with combination therapy.<sup>4</sup> Frequently, a transient lymphocytic thyroiditis occurs, which usually does not require treatment (although propranolol may be indicated occasionally for tachycardia or anxiety). More commonly, hypothyroidism occurs (which may or may not be preceded by hyperthyroidism) and tends to require lifelong thyroid hormone replacement. Preexisting thyroid antibodies seem to correlate with the onset of hypothyroidism.<sup>54</sup>

In addition, pituitary or adrenal insufficiency may arise. Hypophysitis (inflammation of the pituitary) is a condition that is observed almost exclusively with anti-CTLA-4 therapy, and may arise in up to 10% of patients treated with combination PD-1/CTLA-4 blockade.<sup>4</sup> Patients may present with either symptoms of pituitary engorgement (headache, rarely double vision) and/or adrenal insufficiency. Studies have suggested that patients may simply be treated with steroid replacement, although a brief course of high-dose steroids may alleviate compressive symptoms in affected patients.<sup>55</sup> Patients tend to require lifelong steroid replacement. Primary adrenal insufficiency is treated similarly with hormone replacement therapy. Finally, type 1 diabetes may rarely (<1% incidence) complicate therapy, and requires insulin supplementation, typically without steroids.<sup>56</sup> The endocrine toxicities all tend to require long-term (likely lifelong) hormone supplementation, because the initial inflammation seems to "burn out" the hormone-secreting cells.

**TABLE II.** Clinical factors guiding decision on whether to rechallenge with ICIs

Factors that argue against rechallenge	Factors pushing toward rechallenge
<ul style="list-style-type: none"> <li>• Severe or life-threatening toxicity</li> <li>• Steroid-refractory events or need for a second-line immunosuppressant</li> <li>• Prolonged duration of therapy before irAE onset</li> <li>• Cancer progression while on therapy</li> <li>• Complete or near-complete response already realized</li> </ul>	<ul style="list-style-type: none"> <li>• Very short duration of therapy, irAE occurring within the first few cycles</li> <li>• Recurrence of cancer after an extended treatment-free period</li> <li>• Mild toxicity</li> <li>• Diagnostic uncertainty</li> </ul>

### Myocarditis

Among the most ominous and lethal toxicities, myocarditis occurs in up to 1% of treated patients. Myocarditis tends to arise early on therapy (within the first month after starting) and is associated with frequently fulminant and progressive arrhythmias and less commonly cardiomyopathy.<sup>16</sup> Troponin elevation is quite sensitive, and the diagnosis may be confirmed with cardiac magnetic resonance imaging or myocardial biopsy, although given the limitations of these tests, patients with arrhythmias and elevated troponin may need empiric treatment.<sup>57</sup> Of interest, this entity frequently presents concurrently with skeletal muscle inflammation and a myasthenia gravis–like syndrome. The fatality rate is up to 50% in one series,<sup>58</sup> which might be mitigated by pulse doses of steroids (eg, methylprednisolone 1 g daily)<sup>59</sup> plus other immunomodulators (eg, intravenous immunoglobulin, mycophenolate mofetil, or abatacept)<sup>60</sup> although the optimal regimen is not well known.

### Neurologic toxicities

A spectrum of neurologic events may complicate therapy, occurring in up to 5% of patients in aggregate. These arise in 4 general categories: (1) meningo-encephalitis, (2) myasthenia gravis, (3) peripheral neuropathies (including Guillain-Barre syndrome), and (4) central nervous system vasculitis.<sup>61</sup> These syndromes generally mimic their non-ICI analogues, and are treated with high-dose steroids plus appropriate adjunctive treatments in conjunction with neurology consultation (eg, plasmapheresis for Guillain-Barre syndrome). One notable exception is the myasthenia gravis–like syndrome: approximately half the patients have acetylcholinesterase antibody positivity, and seem to have more classical myasthenia.<sup>62</sup> The remaining patients have a myasthenia-like phenotype, which seems to be caused by severe myositis (with elevated creatinine kinase and negative antibody testing), suggesting a distinct clinical syndrome.

### Rheumatologic toxicity

A spectrum of rheumatologic events may occur, most commonly inflammatory arthritis. These patients may have involvement in any joint including knees (more common with combination) or small joints (more common with anti-PD-1).<sup>63</sup> Mild events may be managed with anti-inflammatories; low- or high-dose steroids may also be effective. Steroid-refractory events may respond to methotrexate or TNF inhibitors. A subset of patients develop chronic inflammatory symptoms.<sup>64</sup> Other rheumatologic events may also occur, including Sicca syndrome, scleroderma, and psoriatic arthritis.

### Other toxicities

Essentially any organ system may be affected from ICI toxicities. Other key events to be aware of include

uveitis, gastritis, pancreatitis, mucositis, orchitis, and hematologic toxicities (immune thrombocytopenic purpura, hemolytic anemia, hemophilia, aplastic anemia, hemophagocytic lymphangiohistiocytosis).

### Hypersensitivity reactions/anaphylaxis

Hypersensitivity reactions including anaphylaxis are increasingly recognized risks of high-molecular-weight mAb therapies, including ICIs.<sup>65</sup> Although treatment-related and immunologically mediated, their mechanisms are distinct from those of iRAEs in that they are generally unrelated to the “on-target” effects of the drugs, and on the whole may occur with less frequency. Unlike iRAEs, immediate hypersensitivity reactions may be overcome in the appropriate clinical setting through rapid drug desensitization.<sup>66</sup> It remains unclear whether underlying tendency to hypersensitivity could be unmasked with ICIs, although our anecdotal experience does not suggest that this is a common problem.

Infusion reactions are extremely rare with most ICIs although usually low-grade events (characterized by flushing, rash, fever, rigors, chills, dyspnea, and mild hypotension) may occur in up to 10% to 20% of patients treated with avelumab.<sup>67</sup> Infusion reactions are likely related to a cytokine release endotype, though a mixed mechanism that also includes mast cell activation is possible.<sup>67</sup> These are generally managed by slowing the infusion, or interrupting and restarting at a slower rate, and premedication with antihistamines. In refractory instances, desensitization could also be considered.

### Other safety concerns

Many clinically relevant populations were excluded from ICI clinical trials, including those with dysregulated immune systems (eg, autoimmune disease and organ transplant), immune suppression (eg, chronic viral infection and chronic immunosuppressant administration), or difficulty monitoring (eg, organ dysfunction). Although a full summary of these conditions is beyond the scope of this review, use of ICIs in many of these conditions appears to be fairly safe. For example, patients with preexisting autoimmune disease do appear to have a somewhat increased risk of autoimmune flares, but these are manageable, extremely rarely associated with fatalities, and associated with similar cancer response rates with the general population.<sup>68-71</sup> Similarly, organ dysfunction appears to be safe, although response rates might be slightly lower than in unselected patients.<sup>72</sup> Infections do not seem to be increased by PD-1/PD-L1 or CTLA4-targeting ICIs, though persistent use of corticosteroids or steroid-sparing agents for treatment of iRAEs may increase infection risk (ie, *Pneumocystis pneumonia*).<sup>73</sup> Chronic viral infection, including HIV and hepatitis B and C, do not appear to be associated with increased safety concerns.<sup>74,75</sup> The safety profile of ICIs in patients with acute viral infection, such as

coronavirus disease 2019, the disease caused by severe acute respiratory syndrome coronavirus 2, is also unclear, with early reports showing no obvious safety signals (although more data are needed).<sup>76,77</sup> However, preexisting steroid use is correlated with lower response rates.<sup>78</sup> Patients with solid-organ transplant treated with ICIs (particularly anti-PD-1) have a strikingly high rate of organ rejection, thus making this one of the few near-absolute contraindications for ICI therapy.<sup>79</sup> Kidney transplant recipients must consider the risk of returning to dialysis, because up to one-third may have allograft failure.<sup>80</sup>

### The verdict: Can the patient be rechallenged?

Deciding whether to rechallenge a patient with ICIs when they have developed an adverse event is a complex one (Table II). First, a number of studies have shown that a toxicity with one class of ICI (CTLA-4 vs PD-1/PD-L1) does not seem to correlate with recurrence with the other class.<sup>69</sup> Although this is applicable only to melanoma, we have also observed that toxicities with combination PD-1/CTLA-4 blockade recur in the minority (~20%) of patients who reinitiate anti-PD-1 alone.<sup>81</sup> Another consideration is whether rechallenge is even needed. A growing body of evidence has shown that many patients who discontinue therapy early for toxicity have equivalent outcomes to those not stopping for toxicity.<sup>82</sup> Factors that would push away from rechallenge include (1) severity of toxicity (with life-threatening events being a near-absolute contraindication), (2) steroid-refractory events, (3) longer duration on therapy (suggesting that whatever benefits are to be gained have already been realized), (4) progression of disease, and (5) complete or near-complete response. Factors that might suggest rechallenge include (1) very short duration on therapy (eg, 1-2 doses, suggesting that additional therapy may be needed), (2) recurrence of disease after an extended duration off therapy (eg, drug is stopped for toxicity during an ongoing response, then 12 months later the disease progresses), and (3) clinically mild toxicity or diagnostic uncertainty. In addition, any other concurrent insults that might predispose to the toxicity (eg, omeprazole and interstitial nephritis) should be removed.

Some retrospective studies have been done to provide some insight. Among 167 patients with ICI-colitis who were re-treated, only 32% recurred with ICI rechallenge, although the risk was much higher in patients who required immunosuppression or who had extended duration of symptoms.<sup>83</sup> No fatal events occurred, and less than 10% required infliximab or other immunosuppressants in addition to steroids. Among 40 patients who stopped treatment early for various toxicities and were rechallenged after a median of 3.8 weeks off therapy, 45% had no further irAEs, and 42.5% had recurrence of the same event. No fatal events occurred, and the grading of the events was similar.<sup>84</sup>

In a multicenter retrospective study of 138 cases of ICI-AKI, 31 patients (22%) were rechallenged with an ICI at a median of 1.8 months (interquartile range, 1.2-11.0 months) after the diagnosis of ICI-AKI.<sup>56</sup> Most patients were rechallenged with the same ICI agent, and 39% of patients were receiving steroids (median dose, 10 mg/d) at the time of rechallenge. Recurrent ICI-AKI occurred in only 7 (23%) rechallenged patients. Patients who developed recurrent ICI-AKI had a shorter latency period between the initial AKI episode and rechallenge (1.4 vs 2.1 months). It is very reassuring that of those who developed recurrent AKI, the overwhelming majority again had full (71%)

or partial (14%) recovery of kidney function when re-treated with corticosteroids.

## CONCLUSIONS

Toxicities from ICIs remain a challenging problem that may limit the transformative anticancer benefits of ICIs in some patients. Developing rigorous, evidence-based guidelines for their management has been a challenge, in part due to the diverse presentations and uncommon nature of each individual toxicity. In addition, combination regimens with immune/immune, immune/chemotherapy, and immune/targeted therapy combinations makes diagnostic evaluations more challenging, given the diverse array of toxicities occurring with these agents. Furthermore, novel immunotherapy agents are being developed rapidly, including those targeting alternative T-cell checkpoints (eg, T-cell immunoglobulin and mucin-domain containing-3, lymphocyte activation gene-3, and V-domain Ig suppressor of T-cell activation), natural killer cells (eg, NK2GA and KIR), and alternative immunotherapies (eg, chimeric antigen receptor T cells, tumor-infiltrating lymphocytes, and cancer vaccines),<sup>85</sup> which may present with their own unique patterns of irAEs. Deciding when to rechallenge patients following toxicities remains an individualized decision based on disease status, toxicity severity, and patient risk-tolerance. Ultimately, better biomarkers or clinical risk factors are needed to help individualize this decision.

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