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Updates in toxicities associated with immune checkpoint inhibitors

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Abstract

Introduction—Immune checkpoint inhibitors (ICIs) have become a pillar of treatment for numerous cancers with increasing use in combination with other ICIs and in earlier stages of disease treatment. Though effective, ICI use is accompanied by a milieu of potentially bothersome or even life-threatening toxicities known as immune-related adverse events (irAEs), necessitating careful monitoring and early intervention.

Areas covered—In this review, we provide an overview of recent advances surrounding toxicity pathophysiology and treatment in the context of relevant organ systems. An emphasis on current treatments by toxicity, as well as updates on steroid-refractory toxicities, chronic toxicities, and biomarkers will be a focus of this update on the current understanding of irAEs.

Expert opinion—ICI toxicities are a major limitation on the deployment of multi-agent ICI regimens, and are thus a major priority to understand, treat, and prevent. Recent developments have led to greater understanding of the pathophysiology of these events, which may lead to improved prevention or mitigation strategies. Further, early studies have also suggested steroid-sparing approaches may be useful. Ultimately, preventing and managing irAEs will be a key goal towards successful ICI treatment across a broader range of patients with cancer.

Keywords

Immune Checkpoint; Anti-PD-1; Anti-PDL1; Anti-CTLA4; Immune-related adverse event; Toxicity; Treatment; Steroid-refractory; Biomarkers; Autoimmune inflammation

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Declaration of interest

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1. Introduction

Immune checkpoint inhibitors (ICIs) have dramatically transformed the landscape of cancer treatment beginning with the approval of the first ICI ipilimumab, targeting cytotoxic T lymphocyte antigen 4 (CTLA4) [1]. Since initial approval, further ICIs targeting a variety of cell-surface molecules including programmed cell death-1 receptor (PD-1) and programmed cell death-1 receptor ligand (PD-L1) have become pillars of cancer treatment. More recently, in March of 2022, the lymphocyte activation gene-3 (LAG-3) inhibitor, relatlimab, was approved for use in combination with the PD-1 agent nivolumab to treat unresectable or metastatic melanoma [2,3]. PD-1 agents have been approved for use in 19 cancer types, with variable efficacy among different cancers [1]. Response rates for these commonly used ICIs range from approximately 80% in Hodgkin Lymphoma to 15% to 50% in various solid tumors [4]. In advanced melanoma, PD-1 agents have demonstrated response rates of approximately 45%, which increase to nearly 60% when combined with CTLA4 blockade but decrease to 20% with single agent ipilimumab [5]. Combination PD-1/LAG-3 blockade has also demonstrated increased efficacy compared with anti-PD-1 monotherapy [2,3,6,7]. In numerous cancer types, combinations with either cytotoxic chemotherapy or targeted therapies are playing a growing role. The use of ICIs has expanded beyond metastatic disease, as ICIs are now being increasingly used in adjuvant and neoadjuvant settings. As the menu of ICIs available for use alone, in combination, and earlier in the disease course expands, the risk of immune-related adverse events (irAEs) remains a concern. For example, though toxicity profiles for the PD-1 agents pembrolizumab and nivolumab are similar in both the adjuvant and metastatic settings, the risk of severe, grade 3 or higher toxicities increases from around 20% to 40–50% when these agents are used in combination with CTLA4 blockade [4,8]. Similarly, combination of PD-1/LAG-3 blockade has demonstrated an increased risk of severe toxicity when compared to single-agent PD-1 blockade, though to a lesser degree than that of PD-1/CTLA4 blockade [7]. Severe irAEs can be life-threatening and can disrupt or completely halt treatment. This review intends to summarize basic principles related to the pathophysiology and treatment of irAEs and provide an update on irAEs by organ system affected.

2. Why do toxicities occur?

The targets of ICIs—immune checkpoints— are physiologic mechanisms that serve to downregulate T-cell activation and maintain self-tolerance. The PD-1, PD-L1, CTLA4, and LAG-3 checkpoint molecules mediate this process by influencing both CD4+ and CD8+ T-cells. Under normal circumstances, the PD-1 molecule is expressed by activated T-cells, B-cells, and myeloid cells whereas CTLA4 is expressed only on T-cells [9]. Binding of CTLA4 to its ligand, CD80, prevents interaction between CD80 and the costimulatory receptor CD28, thus regulating priming of naïve T-cells, while interaction between PD-1 and its ligands, PD-L1 or PD-L2, primarily dampens activity of effector T-cells to maintain peripheral tolerance. The LAG-3 molecule normally regulates T-cell function through various mechanisms, including interaction with MHC II to down-regulate cytokine secretion and proliferation of CD4+ T-cells, direct inhibition of CD8+ T cells, and enhancement of regulatory T cell (Treg) immunosuppressive activity [2]. Both CTLA4 and PD-1 expression is upregulated via T-cell activation, while PD-L1 expression is upregulated by inflammatory

cytokines such as interferon-gamma, together dynamically balancing T-cell activation and preventing autoimmune inflammation [10]. Tumor-mediated chronic inflammation can thereby result in increased expression of PD-1 and PD-L1. Tumor cells can further exploit these physiologic checkpoint mechanisms by expressing PD-L1 to quell anti-tumor immune responses through promotion of T-cell exhaustion [4]. ICI blockade of these checkpoints results in a disinhibited immune response to promote desired antitumor activity and high levels of PD-L1 expression by tumors is associated with higher response rates to treatment with anti PD-1/PD-L1 agents [11]. However, the process of checkpoint blockade can also promote loss of self-tolerance and subsequent response to self-antigens manifesting as autoimmune toxicities, or irAEs. irAEs can affect virtually any organ and more commonly occur with combination PD-1/CTLA4 blockade or ipilimumab alone than with single agent PD-1 or PD-L1 immunotherapy [12]. While the basic mechanisms of ICI toxicities are well understood (loss of self-tolerance leading to autoimmune-like complications), specific mechanisms remain less clear (e.g. why one patient experiences a particular toxicity rather than a different irAE or none at all). Several studies have suggested this may be related to common antigens shared between tumor and affected tissues, pre-existing subclinical autoimmunity unleashed by ICI therapy (and potentially detected by antibodies), viral infection, microbiome composition, and other putative mechanisms [13]. Currently, identifying reliable biomarkers to predict which patients will experience severe toxicities remains an urgent need, as does identifying approaches to prevent these events.

3. Grading

irAEs vary in severity from mild, moderate, to severe and can be classified as grade 1 through grade 5 using the standardized Clinical Criteria for Adverse Events (CTCAE). Generalizing, grade 1 toxicities are considered mild and can be asymptomatic, and grade 2 toxicities are moderate. Grade 3 and higher toxicities are severe with grade 4 toxicities having immediate, life-threatening consequences. Death due to an adverse event is considered a grade 5 event [14].

4. Treatment principles

Toxicity grade helps guide treatment and monitoring of irAEs as well as potential cessation of ICI therapy. Treatment guidelines are more fully outlined in society guidelines, including American Society for Clinical Oncology, Society for ImmunoTherapy in Cancer, and National Comprehensive Cancer Network [15–17]. Any new symptoms or lab abnormalities following ICI initiation should be closely monitored under the suspicion for irAEs. For most mild, grade 1 toxicities, ICI treatment can be continued along with symptomatic support, such as topical emollients or topical corticosteroids for pruritis or loperamide for mild diarrhea. ICI treatment may be held for grade 2 toxicities, with resumption when the toxicity grade regresses to grade 1 severity. Administration of corticosteroids at 0.5–1 mg/kg/d of prednisone may be considered for grade 2 toxicities when more symptomatic, severe, or persistent. ICI treatment should be held for severe, grade 3–4 toxicities with initiation of high dose corticosteroids at 1–2 mg/kg/d of prednisone. Steroids are typically tapered over 4–6 weeks. For unremitting symptoms, additional agents, such as infliximab, mycophenolate mofetil, rituximab, vedolizumab, or intravenous immunoglobulin may be

considered depending on toxicity and are further detailed in the sections below and in Table 1. While ICI rechallenge can be considered following complete or near-complete (grade 1) resolution of grade 3 toxicities in certain cases, permanent cessation of ICI therapy is recommended for grade 4 toxicities, except in cases of endocrine toxicity which are generally well-managed with hormone replacement [15].

5. Updates on types of toxicities

5.1 Cutaneous Toxicities

Cutaneous adverse events from ICIs are among the most frequently encountered toxicities with treatment, with rates ranging between 30–60% [18]. PD-1 and PD-L1 ICIs are associated with lower rates of cutaneous toxicities when compared with CTLA4 monotherapy or combined PD-1/CTLA4 therapy [5]. Cutaneous irAEs include a wide range of presentations and are thought to be mediated by auto-reactive T-cells when self-tolerance promoting pathways are blocked with ICIs. Ultraviolet skin damage exposing self-antigens and T-cell cross-reactivity between tumor and skin antigens have also been implicated in the pathogenesis of skin manifestations [18]. A link between allergic conditions and cutaneous irAEs has also been suggested, with one study finding increased risk for cutaneous irAEs (OR 1.95) in patients with one drug allergy and increased risk of severe irAEs (OR 6.57) in patients with three or more drug allergies [19].

Examples of cutaneous irAEs include pruritis, eczematous dermatitis, and lichenoid reaction. Preexisting psoriasis may commonly worsen, though it can also arise in patients without a history of psoriasis and develops later in the treatment course when compared to other cutaneous toxicities [20,21]. A study of 76 ICI-treated melanoma patients with pre-existing psoriasis found that 57% of patients experienced a flare, with significantly longer progression-free survival in those patients; flares were generally manageable with standard therapies and rarely required discontinuation [21]. Other cutaneous effects include vitiligo, autoimmune bullous disorders such as bullous pemphigoid (BP), and very rarely, severe life-threatening reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) [22].

Development of cutaneous irAEs has been associated with improved responses to ICIs [23]. In a recent study examining the effect of eczema, lichenoid reaction, and vitiligo-like depigmentation in patients receiving PD-1 agents for stage IIC-IV melanoma, patients who developed at least 1 of these 3 irAEs were half as likely (HR 0.460) to experience disease progression [24]. Similarly, vitiligo has previously been associated with survival benefit in patients receiving ICIs for advanced melanoma [25,26]. Though vitiligo is a less common irAE across all cancers, it is more commonly observed in melanoma, particularly when treated with CTLA4 agents, and is reported at rates ranging from 7% to 12% [18,20]. One study of the real-world incidence of vitiligo reported 89.5% of ICI vitiligo cases arising in patients with melanoma from a total vitiligo rate of 0.7% in all cancers [27].

While many cutaneous irAEs occur early in treatment, toxicities such as vitiligo, BP, or alopecia areata can occur months after treatment initiation requiring continual monitoring.

Severe toxicities, such as Stevens-Johnson syndrome and toxic epidermal necrolysis most commonly occur around 1 month from therapy initiation [28]. As with all irAEs, management of cutaneous irAEs is guided by toxicity grade and response to supportive and initial treatment measures and is aided by early involvement of dermatologists. Evaluation of cutaneous irAEs by dermatologists has been associated with improved survival and increased treatment of irAEs [29].

Mild inflammatory dermatitides (grade 1) can be treated with topical emollients or mild-to-moderate potency topical steroids without cessation of therapy or use of systemic corticosteroids. As severity increases to moderate severity (grade 2) pausing ICI therapy may be considered. The addition of systemic corticosteroids is also considered if additional supportive measures such as oral antihistamines or other topical agents (e.g. medium-to-high potency corticosteroids, menthol, pramoxine) fail to improve symptoms. Grade 3 or 4 dermatitides require cessation of ICI therapy with systemic corticosteroids, with permanent cessation in the case of grade 4 toxicities. Adjunctive therapies for symptoms of pruritis include phototherapy, gabapentin, aprepitant, and biologics like omalizumab or dupilumab. ICI psoriasis is frequently managed with topical steroids. Though unlike de novo psoriasis, the addition of systemic corticosteroids is considered for higher grades. Additional agents such as acitretin, phototherapy, methotrexate, apremilast, and biologics may be used [30,31]. Management of mild bullous cutaneous irAEs similarly involves stepwise escalation of topical to systemic steroids and steroid-sparing agents with special attention to wound care for unroofed bullae. Steroid sparing agents, such as intravenous immune globulin (IVIG) or rituximab may be used. The IL-4 receptor antagonist, dupilumab, has also shown promise in treating BP in case reports [32]. Severe cutaneous adverse reactions, such as SJS or TEN should be managed in an inpatient setting with IV corticosteroids and supportive care aimed at preventing infection and electrolyte aberrancies due to loss of the skin barrier, with potential addition of cyclosporine, infliximab, or IVIG [15,17].

5.2 Endocrine Toxicities

Endocrine irAEs are common and include thyroiditis and subsequent hypothyroidism, hypophysitis, primary adrenal insufficiency, or insulin-deficient diabetes. Endocrine toxicities differ in management from most irAEs, as they do not typically require permanent drug discontinuation or high-dose steroids. Rather, treatment is directed at hormone replacement for deficiencies resulting from destruction of hormone-producing cells that occurred largely prior to toxicity detection.

5.2.1 Hypophysitis and Primary Adrenal Insufficiency—

Hypophysitis is an irAE that frequently results in central hypothyroidism, central adrenal insufficiency, and hypogonadism, and it often necessitates persistent hormone replacement despite resolution of active inflammation [33]. Hypophysitis is classically associated with the ICI ipilimumab, though can occur with other ICIs. A recent retrospective study of the development of hypophysitis on the PD-1 agents pembrolizumab and nivolumab found phenotypic differences between hypophysitis due to ipilimumab and PD-1 agents. Hypophysitis due to the studied PD-1 agents occurred at rates of 0.05% (compared with 13.6% on ipilimumab), had later onset, decreased rates of pituitary enlargement (28% versus 98% with ipilimumab)

and more commonly resulted in central adrenal insufficiency without other anterior pituitary hormone deficiencies [34]. The predilection for hypophysitis to develop on ipilimumab is likely due to ectopic expression of CTLA4 on pituitary cells, as demonstrated by mRNA and protein levels from murine and human pituitary glands. The development of pituitary antibodies has also been associated with hypophysitis, with studies demonstrating association of pituitary antibodies (against TSH, FSH, and/or ACTH secreting cells) in hypophysitis patients previously negative at baseline and increases in anti-GNAL and anti-ITM2B antibodies with the development of this irAE [35,36]. Primary adrenal insufficiency (PAI) is another rare but often severe irAE. A pharmacovigilance analysis of ICI-associated PAI found that onset of this toxicity is variable, ranging from 6 to 576 days to onset (median 4 months) and is severe in 90% of cases [37]. Though autoimmune adrenal insufficiency is often associated with antibodies to the adrenal cortex, adrenal antibodies have been noted in a minority of case reports of ICI-induced PAI [37].

Routine monitoring for pituitary or adrenal irAEs is not always conducted and varies by practice. Management of central or primary hormone deficiencies is achieved with hormone replacement dependent upon deficiencies identified. Mild to moderate adrenal insufficiency is managed with corticosteroids, such as hydrocortisone or prednisone, with higher stress-dosed corticosteroids if severe. In the case of primary adrenal insufficiency, fludrocortisone is also utilized. Mild hypophysitis may be treated with testosterone or estrogen therapy when indicated for hypogonadism, as well as with thyroid replacement. Short-term high dose steroids are used in the setting of severe hypophysitis with neurologic symptoms or significant pituitary swelling on MRI [15,38].

5.2.2 Thyroiditis—Thyroid toxicity is the most common endocrine irAE, most frequently reported with combination PD-1/CTLA4 blockade and PD-1 agents alone, with rates as high as 40–50% in observational studies [39]. Thyrotoxicosis is a common presentation which may progress to hypothyroidism, particularly when overt thyrotoxicosis is present, and euthyroid recovery is more likely in those presenting with subclinical thyrotoxicosis [40]. Overt thyrotoxicosis has also been associated with longer overall survival, longer progression free survival, and with anti-thyroid antibodies. Presence of anti-thyroid antibodies in up to half of patients with overt thyrotoxicosis suggests separate mechanisms by which overt thyroid toxicity occurs when compared with subclinical presentations, though the pathophysiology behind these irAEs has not been fully elucidated [41]. Of note, anti-thyroid antibody positivity at baseline was associated with increased overall incidence of thyroid irAEs in patients treated with combination PD-1/CTLA4 blockade and PD-1 monotherapy, with incidence increasing from 4% to 32.2% and 23.5% to 60% in the monotherapy and combination therapy groups, respectively [42]. Interestingly, while presence of baseline anti-thyroid antibodies correlated to the development of thyroid irAEs in patients on PD-1 monotherapy, no difference in baseline anti-thyroid antibody status was found between patients treated with PD-1/CTLA4 therapy who did and did not develop thyroid irAEs [42].

Monitoring of thyroid function with a TSH level every 4–6 weeks while on therapy should be performed. For hypothyroidism, thyroid hormone replacement is initiated in symptomatic patients or in asymptomatic patients when TSH is persistently elevated >10mlU/L. In

thyrotoxicosis, symptom management is achieved (when needed) with beta-blocking agents and supportive care. Severe (grade 3–4) thyrotoxicosis may require anti-thyroid medications, such as methimazole, propylthiouracil, or thyroid ablation. Rarely, short-term corticosteroids may be used in the acute setting [15,38,39].

5.2.3 Diabetes Mellitus—Insulin-deficient diabetes mellitus is a rare irAE that virtually always occurs in the setting of PD-1/PD-L1 therapies rather than CTLA-4 blockade [43]. It is thought to occur via rapid immune-mediated destruction of beta islet cells, though may be mechanistically distinct from type 1 diabetes in that islet auto antibodies have been reported in lower frequencies than in classic T1DM [43,44]. Greater PD-L1 expression in T1DM patients has been demonstrated, highlighting the role of the PD-1/PD-L1 pathway in modulating an inflammatory response in the pancreas [44]. Genetic factors may also influence the risk of ICI-induced diabetes, with human leukocyte antigen (HLA) haplotypes, such as HLA-DR4, associated with susceptibility to T1DM identified in a majority of studied patients with ICI-induced diabetes [38,43]. This toxicity can frequently present with severe symptoms of diabetic ketoacidosis (64/91 patients in one review) and monitoring of blood glucose at the time of treatment administration is helpful in identifying this potential irAE [43]. Management consists of indefinite insulin therapy and correction of immediate fluid and electrolyte imbalances if presenting in DKA [38].

5.3 Gastrointestinal Toxicities

5.3.1 Colitis—Diarrhea and colitis are frequently encountered irAEs that can be serious and life-threatening. ICI enterocolitis most commonly occurs in patients receiving combination PD-1/CTLA4 therapy, with mild diarrhea in almost half of patients and severe colitis in 15–20% of patients [45,46]. The development of ICI colitis has been recently better understood to be related to expansion of interferon-gamma producing CD8+ tissue resident memory T cells, increased CTLA4+ Treg cell proliferation, and macrophages expressing inflammatory chemokines to induce recruitment of CD4+ and CD8+T cells to colonic tissue [45,47,48]. Most often, ICI colitis results in inflammation of the colon demonstrated via endoscopic evaluation, though absence of mucosal inflammation is seen in up to 30% of patients presenting with colitis symptoms [46]. Endoscopic findings of mucosal injury have been associated with responses to treatment with systemic corticosteroids (though ulceration may predict need for additional immunosuppressive agents, such as infliximab), while findings of microscopic colitis have been correlated to response to budesonide therapy, underscoring the importance of endoscopic evaluation in management [49,50]. Vitamin D use has been associated with decreased incidence of ICI colitis in a retrospective analysis of 213 ICI-treated melanoma patients [51].

Mild (grade 1) diarrhea can be managed symptomatically with agents including loperamide or diphenoxylate-atropine, without necessitating discontinuation of ICIs. Endoscopy is warranted when symptoms become severe and infectious causes have been excluded. ICI therapy is held and systemic high-dose corticosteroids are administered for grade 2 or higher ICI colitis, though 30–40% of patients with gastrointestinal irAEs require secondary immune suppression [52]. Infliximab and vedolizumab can be utilized in the event of steroid-refractory toxicity; severe ulceration on endoscopic evaluation appears to predict

need for these agents. If a response with these additional agents is not achieved, infectious etiologies should be reconsidered prior to consideration of surgery or fecal microbiota transplant [53]. Microscopic colitis may be treated with mesalamine or budesonide prior to escalation to corticosteroids and biologic agents [53,54].

5.3.2 Hepatitis—ICI hepatotoxicity is another irAE that can arise from loss of self-tolerance and is mediated by cytotoxic T cells. Though similar in presentation, ICI hepatitis differs from autoimmune hepatitis in that antibodies against the liver are not usually found [55]. Less than 5% of patients on ICI monotherapy develop hepatitis, though the incidence of this irAE increases to almost 25% in patients on combined PD-1/CTLA4 therapies [52]. ICI hepatitis incidence is also increased with combined ICI/chemotherapy regimens [53]. Use of acetaminophen and HMG-Co-A reductase inhibitors has been associated with increased risk of ICI hepatotoxicity [56]. Routine monitoring of liver blood tests (AST, ALT, bilirubin, alkaline phosphatase) before each infusion of therapy is recommended and can detect asymptomatic cases of hepatitis. Grade 1 hepatitis may be observed with increased monitoring of laboratory values 1–2 times weekly. ICI therapy should be held for grade 2 hepatitis and higher, with administration of corticosteroids if no improvement is seen or toxicity is severe. If steroid-refractory, additional agents used include mycophenolate mofetil, tacrolimus, azathioprine, or, in the case of fulminant hepatitis, anti-thymocyte globulin [52,53].

5.4 Pneumonitis

Pneumonitis is an irAE that is more common in PD-1/PD-L1 monotherapy and PD-1/CTLA4 combination therapy than with CTLA4 monotherapy, with variable reported incidence between 3% and 11% [57]. It is seen more frequently in patients with non-small cell lung cancer and renal cell carcinoma [57,58]. Though commonly a mild-to-moderate (grade 1–2) irAE, pneumonitis can be fatal. While other events (e.g. myocarditis) may have higher fatality rates, pneumonitis appears to cause the most total fatalities (particularly in patients treated with anti-PD-1/PD-L1 monotherapy) due to its somewhat common nature and potential for fatalities [59,60]. Further, higher rates of fatality in patients with lung cancer from pneumonitis have been reported, with faster time-to-onset of fatal pneumonitis when compared to non-fatal cases [61]. Pneumonitis develops from T-cell reactivity to autoantigens though its exact pathogenesis is likely multi-faceted and not completely elucidated. Higher ratios of Th1 and Th17 cells compared to Treg cells and increased levels of IL-17 and IL-35 in the blood and bronchoalveolar lavage fluid of patients with ICI pneumonitis suggests an imbalance of effector and regulatory T-cells may contribute to its pathogenesis [62]. Diagnosis is aided by computed tomography (CT), with radiographic subtypes on imaging including ground glass opacities, cryptogenic-organizing pneumonia-like, interstitial, hypersensitivity, and pneumonitis not otherwise specified [63]. Radiographic features have been associated with pneumonitis severity and can inform management [60]; an example of pneumonitis is shown in Figure 1. Patients with symptoms of pneumonitis (grade 2 and above) should be started on systemic corticosteroids and ICI therapy should be held. If symptoms do not improve or worsen within 48 hours, the irAE is considered as steroid-refractory. As such, additional immunosuppressive agents including

mycophenolate mofetil, cyclophosphamide, IVIG, infliximab, or tocilizumab may be added [15,60].

5.5 Rheumatologic toxicities

5.5.1 Arthritis—Rheumatologic toxicities encompass a wide range of diagnoses and include inflammatory arthritis, polymyalgia rheumatica, myositis, sicca syndrome, and rarely vasculitides or other rheumatic diseases like scleroderma. Inflammatory arthritis (IA) is the most common rheumatologic irAE, occurring in approximately 3–7% of patients [64]. While IA can present with polyarthritis similar to rheumatic arthritis, a difference in their pathogenesis is suggested by anti-cyclic citrullinated peptide (anti-CCP) seronegativity in ICI IA. A recent observational study of 34 patients found that patients largely do not become seropositive for anti-CCP antibodies when followed for up to 24 months [65]. A prior review reported anti-CCP positivity in 9% of cases of inflammatory arthritis [66]. However, a subset of 79 ICI IA patients (11.9%) were found to have anti-RA33 antibodies, compared with 0 patients on ICI without IA, and may be of future interest in predicting risk for ICI IA [67].

Management of mild inflammatory arthritis with non-steroidal anti-inflammatory drugs is common, while moderate inflammatory arthritis symptoms may require corticosteroids or other steroid-sparing agents such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, and biologics including TNF-inhibitors and IL-6 antagonists [68]. Of note, even with cessation of ICI therapy, symptoms of ICI IA may persist, with an observational study finding active IA in 70% and nearly 50% of patients at 3 and 6 months after ICI cessation, respectively [69]. More research is needed to study ongoing management of ICI IA and whether ongoing biologic and ICI therapy may be safely and effectively given concurrently.

5.5.2 Myositis—Compared with other rheumatologic complications, myositis is an irAE with a higher risk of rapid worsening or death caused by diaphragm involvement or concurrent myocarditis. As such, early high dose steroids are a mainstay of treatment with additional therapies like IVIG or plasmapheresis in severe cases. Myositis is seen with earlier time-to-onset compared with other rheumatologic irAEs and can be found in isolation, with a myasthenia gravis-like presentation, or with myocarditis, the latter of which doubles the fatality rate in one series (24% versus 56.7%.)[70]

5.6 Myocarditis

Though rare, ICI myocarditis accounts for approximately half of major adverse cardiac events from ICIs, with left ventricular dysfunction, arrythmias, accelerated atherosclerosis, acute coronary syndromes, and congestive heart failure making up other reported cardiac irAEs [71,72]. Though the mechanisms by which myocarditis develop are not well understood, infiltration of the myocardium with CD4+ and CD8+ T-cells reminiscent of cardiac transplant rejection have been reported, with shared T-cell receptor (TCR) sequences in skeletal muscle, cardiac muscle, and tumor suggesting reactivity to shared antigens in these tissues [71,73]. A recent study of murine myocarditis clonal TCR epitopes found that alpha-myosin was highly recognized by these TCRs, with overlap of alpha-myosin expanded TCR repertoires in human donors with and without ICI myocarditis, suggesting

implication of alpha-myosin in disease pathogenesis [74]. The suspicion for myocarditis should be high with any new cardiac symptoms such as shortness of breath, chest pain, or syncope, and severe myocarditis may present with cardiogenic shock or complete heart block. Elevated troponin levels, electrocardiogram changes, and echocardiographic abnormalities are frequently present, with an interstitial inflammatory infiltrate seen on the gold standard endomyocardial biopsy, though biopsy is not commonly utilized in diagnosis [71,75]. Cardiac MRI is frequently employed in the diagnostic workup, though less sensitive for the diagnosis of ICI myocarditis compared with non-ICI myocarditis [71]. Management of ICI myocarditis involves immediate hospital admission with administration of 1g IV methylprednisolone followed by oral corticosteroids. In steroid-refractory or very severe cases, additional immunosuppressants including mycophenolate mofetil, tacrolimus, anti-thymocyte globulin, abatacept, belatacept, or alemtuzumab are considered [17,71]. The use of infliximab is cautioned against in some guidelines, as it has been associated with higher risk of death from cardiovascular causes [17,76].

5.7 Nephritis

ICI acute kidney injury (AKI) is an irAE that may be diagnostically challenging to distinguish from other causes of AKI in patient populations already at risk for AKI [77]. ICI-AKI occurs in up to 3–5% of patients, with acute tubulointerstitial nephritis (ATIN) the most seen histologic lesion on biopsy resulting from direct renal ICI toxicity [77]. While loss of self-tolerance and T-cell mediated damage likely play a role in development of ICI-AKI, re-activation of primed T-cells from exposure to ATIN-associated drugs may also influence the development of ICI-AKI, with concomitant use of ATIN associated medications (commonly proton pump inhibitors) reported in 62% in ICI-AKI patients [77,78]. Though approximately 65% of patients with ICI-AKI have been demonstrated to have renal recovery following ICI-AKI, absence of renal recovery has been associated with higher mortality [79]. As such, early initiation of corticosteroids is key in the management of ICI-AKI, as steroid initiation within 3 days has been associated with higher odds of renal recovery (OR 2.09) [77]. Of note, a recent study of steroid treatment duration found no significant difference in rates of ICI-AKI recurrence in patients treated with 28 days of corticosteroids compared to those treated for 29–84 days; thus, a shorter course of steroids may be reasonable in these patients [80]. Rates of recurrence of ICI-AKI following ICI rechallenge are reported between 16.5–23% in two multicenter studies of ICI-AKI patients [77,79]. ICI-AKI is often asymptomatic and revealed via urinalysis, quantification of proteinuria, and analysis of urine sediment, with renal biopsy considered in different situations (e.g when alternative etiologies cannot be excluded or when above grade 2 and not uniformly agreed upon in guidelines) [15,17,78]. Management of ICI-AKI includes discontinuation of any ATIN-associated medications and temporary cessation of ICI therapy during evaluation. For ATIN, corticosteroids are administered with the addition of infliximab or mycophenolate mofetil (or azathioprine or cyclophosphamide by some guidelines) if steroid-refractory [78,81].

5.8 Neurologic toxicities

Neurologic irAEs including peripheral neuropathy, cranial nerve palsy, myasthenia gravis-like toxicities of the neuromuscular junction, aseptic meningitis, encephalitis, and hearing

loss are rare but serious consequences of ICIs more common in patients treated with combination PD-1/CTLA4 compared with PD-1 monotherapy [82,83]. Though T-cell mediated cytotoxicity almost certainly contributes to the development of neurologic irAEs, the role of neural autoantibodies is less well defined [84]. ICI-mediated neurologic toxicities frequently resemble de novo neurologic diseases, however irAEs that demonstrate symptoms of diseases like Guillain-Barre, ophthalmoplegia, or autoimmune encephalitis frequently lack positivity for antibodies typically associated with these conditions suggesting distinct pathophysiology [83,85]. Notably, ICI myasthenia gravis has been demonstrated to have acetylcholine receptor (AchR) antibodies, though present at a lower frequency than in de novo myasthenia gravis (57% compared with approximately 85%) [83]. Of neurologic irAEs, myasthenia gravis has the highest fatality rate (nearing 20%) and the most rapid onset following ICI initiation (median = 29 days versus 61–80 days in one pharmacovigilance study) [86]. Compared with de novo myasthenia gravis, ICI myasthenia gravis is rapidly progressive and presents more commonly with bulbar or respiratory symptoms, with nearly half of patients requiring respiratory support [85,87].

Evaluation of neurologic irAEs includes imaging with MRI and CSF studies when meningitis or encephalitis are suspected, often with thyroid, metabolic, and autoimmune antibody panels for encephalitis and cortisol and ACTH for suspected meningitis. Evaluation of peripheral nervous system disorders, such as myasthenia gravis or Guillain-Barre, utilizes nerve conduction studies with antibody testing, blood work (e.g. B12, B6, serum protein electrophoresis), or spinal imaging with lumbar puncture depending on presentation [17]. Due to frequent overlap of ICI myasthenia gravis with myositis and myocarditis, and the significant fatality rate associated with these cooccurring conditions, initial evaluation for suspected ICI myasthenia gravis is accompanied by evaluation of serum troponin, creatine kinase, and EKG [88]. Management of neurologic irAEs is primarily with corticosteroids, though immunomodulatory therapies used in the management of de novo neurologic conditions, like IVIG and plasmapheresis, are also used in conjunction depending on the irAE [83]. For example, IVIG and plasmapheresis are a mainstay in ICI myasthenia gravis and Guillain-Barre, while rituximab may be considered in cases of autoantibody-positive encephalitis or myasthenia gravis refractory to IVIG or plasmapheresis [15,85]. Neuropathic pain is addressed with adjunctive therapies such as gabapentin or duloxetine [15].

5.9 Hematologic toxicities

Among hematologic irAEs, hemolytic anemia and immune thrombocytopenia account for roughly half of observed toxicities, with bone marrow failure, hemophagocytic lymphohistiocytosis (HLH), thrombosis, and other rare toxicities making up the rest of the heme irAE spectrum [89,90]. These irAEs have been more frequently observed in patients on the PD-1 therapies nivolumab and pembrolizumab, compared with ipilimumab-containing mono and combination therapies [90]. Blockade of immune checkpoints leading to synthesis of autoantibodies driven by disinhibited Th2 CD4+ T-cells and direct CD8+ T-cell mediated cytotoxicity are postulated to cause hematologic irAEs such as cytopenias and bone marrow failure, with subsequent stimulation of macrophages to produce IL-6 and IL-8 postulated to be responsible for the pathogenesis of HLH and venous thromboembolism, respectively [89].

Management of these toxicities is dependent on initiation of corticosteroids, holding of ICI therapy, transfusions as necessary, and addition of other agents depending on the cell line impacted and hematologic standards of care. For example, in addition to corticosteroids, hemolytic anemia may be managed with rituximab, IVIG, cyclosporine or mycophenolate mofetil if unresponsive to initial therapy [89]. Similarly, IVIG is considered for severe ITP, granulocyte colony-stimulating factor for neutropenia, and antithymocyte globulin and cyclosporine in the case of aplastic anemia [15,17,89]. Other agents used for HLH include tocilizumab and etoposide [89].

6. Delayed and chronic toxicities

Most irAEs develop within 4–6 months of therapy initiation, though delayed toxicities beyond one year of therapy can also occur and may not be captured in trial data with limited follow up [91]. A multicenter study of 999 melanoma patients estimated the incidence of delayed irAEs to be 5.3%, with greater incidence in those with PD-1 therapy as a later-line therapy, and with majority of delayed irAEs occurring while patients continued therapy [91].

While irAEs have potential for delayed onset, they are more likely to have delayed resolution of symptoms despite discontinuation of ICIs. In a multicenter study of 387 melanoma patients receiving adjuvant PD-1 blockade, chronic irAEs persisting beyond 12 weeks of discontinuation were present in 43.2% of patients [92]. Chronic irAEs were most commonly endocrinopathies, neurotoxicities, ocular events, xerostomia, and arthritis and were low grade. Similarly, another study of various ICI regimens found the rate of unresolved toxicities at a median duration of follow up of almost 2 years to be approximately 65% and 35% in melanoma patients receiving dual ICI and monotherapy, respectively [93]. Radiographic findings of pneumonitis have also been demonstrated to persist or worsen in nearly two-thirds of patients, despite symptom resolution in almost 90% of patients [94]. As effects of irAEs persist, health-related quality of life scores have been demonstrated to be lower than in patients without chronic irAEs [95]. ICIs may also have chronic effects outside of typical autoimmune irAEs. ICIs have been implicated in the progression of atherosclerotic plaques and combination PD-1/CTLA4 blockade has been associated with a rise in systolic blood pressure in patients with at least two years of follow up [96,97]. The potential for ICIs to cause increased obesity-associated inflammation and exacerbate the complications of obesity is also of concern [13]. As the use of ICIs expands and patient survival lengthens, clinically significant long-term effects of ICI therapy, including chronic irAEs and other off-target effects, deserve further exploration.

7. Steroid-refractory toxicities

Corticosteroids are the cornerstone of treatment in virtually all irAEs. However, non-response or inability to taper corticosteroids often warrants additional immunosuppression. Though the proportion of patients experiencing steroid-refractory toxicities is difficult to estimate, rates of refractory toxicities have been reported between 2 and 23%, with higher rates in patients on dual ICI therapy (23% versus 3% in one study), and commonly include colitis, hepatitis, and pneumonitis [98–100]. In a study of steroid-refractory toxicities in which 2% of patients required an additional nonsteroidal immunosuppressant, commonly

TNF-a inhibitors or mycophenolate mofetil, additional agents were given to approximately two-thirds of patients for non-response and one-third for dependence on steroids [99]. Various steroid sparing agents including tocilizumab, the IL-6 receptor antibody, have demonstrated efficacy for the treatment of steroid-refractory toxicities, with recent insights into IL-6 blockade and potential to improve tumor control and mitigate toxicity emerging [101–103].

8. Biomarkers

Further understanding of predictive and prognostic biomarkers of response to ICI therapy has been accompanied with new discoveries in the prediction and prognosis of irAEs [104]. Many existing studies on irAE biomarkers have focused on particular cancers or toxicities, therefore, generalization of what is known may not be possible without further studies [105]. While a full description of all biomarkers under investigation is beyond the scope of this review, we highlight several studies below.

8.1 B cells

Patients with early B-cell changes following combination ICI in melanoma patients, namely a decline in circulating B-cells and an increase in circulating $CD21^{lo}$ B cells, were found to experience higher rates of toxicity. Further, the degree of decline in circulating B cell numbers following treatment was associated with greater maximal toxicity severity as well as quicker time to onset [106]. A study in metastatic renal cell carcinoma patients treated with combination ICI also noted an increase in circulating $CD21^{lo}$ B cells following therapy, though no significant differences in total circulating B cells were discovered. Notably, lower baseline levels of $CD21^{lo}$ B cells were correlated with irAEs [107]. Though these B cell changes do not correlate with response to therapy, their correlation with toxicity supports a role of B cells in toxicity pathogenesis, supported by prior studies of B cell alterations and autoimmunity in CTLA4-deficient humans, and subsequently as a predictive biomarker [106,108].

8.2 T cells

$CD62L^{low}$ CD4+ effector memory T cells have been demonstrated as a potential predictive biomarker for tumor response, with recent potential as a predictive biomarker of irAEs [109,110]. In a study of the peripheral blood of metastatic melanoma patients utilizing mass cytometry, single-cell and bulk RNA sequencing, CD4+ effector memory T cells and increased TCR diversity were found to correlate with severe irAEs and a biomarker score was created [111]. The created model was predictive of severe irAEs independent of parameters such as ICI therapy type, response, age, sex, melanoma type or affected organ system [111]. Further, a recent study correlated subpopulations of T cells with particular irAEs, suggesting different T-cell populations may serve as a predictive biomarker for irAEs with organ-specificity [112]. Findings of this study included that patients experiencing arthritis, pneumonitis, and thyroiditis had baseline differences in levels of CD8+ central memory T cells, CD4+ T_{H2} cells, and CD4+ T_{H17} cells, respectively, when compared to patients without irAEs.

8.3 Other Host Factors—Cytokines, Antibodies, Microbiome, and Genetics

Circulating cytokines and auto-antibodies, along with gut microbiome composition and genetic polymorphisms have all been implicated as promising biomarkers in toxicity development. Analysis of 65 cytokines in plasma samples of PD-1/CTLA4 treated melanoma patients demonstrated that elevated expression levels of 11 cytokines (G-CSF, GM-CSF, Fractalkine, FGF-2, IFNa2, IL12p70, IL1a, IL1B, IL1RA, IL2, and IL13) were associated with high grade irAEs [113]. Additionally, lower baseline levels of IL-6 and higher baseline levels of IL-17, among other cytokines, have been implicated in irAE development [103,113,114]. Anti-thyroid antibodies have been associated with an overt thyrotoxicosis presentation of thyroid irAEs, while other autoantibodies have been correlated to the development of serious toxicities such as pneumonitis and hypophysitis, namely anti-GNAL and anti-ITM2B in hypophysitis and anti-CD74 in pneumonitis [41,115]. Gut microbiome composition has been associated with the development of colitis, with microbial signatures differing in patients who developed severe colitis and irAEs more generally [116,117]. Receipt of antibiotics during therapy has also been correlated to increased risk of irAEs, particularly pneumonitis in patients with lung cancer and colitis [118–120]. Additional validation is needed. In the age of personalized medicine and targeted therapies, single-nucleotide polymorphisms have also been associated with increased odds of developing irAEs in melanoma patients treated with ICIs, some of which have been shown to have overlapping associations with autoimmune diseases [121]. Furthermore, specific human leukocyte antigen (HLA) types have been associated with specific toxicities, such as pruritis, colitis, and insulin-dependent diabetes mellitus [105].

9. Conclusion

As the uses of ICIs expand, the recognition and prompt management of irAEs is critical. irAEs affect a large proportion of treated patients, with the reporting of rare, severe irAEs increasing likely due to increased recognition and volume of patients treated. Challenges in treatment include balancing continued treatment of disease with the use of immunosuppressant medications. New insights into the pathogenesis of toxicities have influenced the use of steroid-sparing agents for treatment of particularly severe or refractory toxicities. The identification of patient-specific biomarkers may aid in the prediction of toxicities and their severities.

10. Expert Opinion

The study of irAEs has produced enormous increases in our understanding of these events, a key need as ICIs are being used increasingly in combination and in earlier stages of disease. Yet the heterogeneity of these events, in terms of phenotype, severity, response to initial therapy, and underlying tumor/subject characteristics makes them more difficult to study in a systematic fashion. Thus, much of our current data relies on anecdote, observational data, and expert opinion.

One major need, therefore, is the generation of more robust, evidence-based data to manage these events. Several studies represent movement in the right direction, including the study of infliximab vs. IVIG in steroid-refractory pneumonitis (NCI-cooperative group

sponsored, NCT04438382), infliximab + steroids vs. steroids alone for upfront colitis treatment (NCT04305145) two studies of abatacept in ICI-myocarditis (NCT05195645, NCT05335928), and others. These studies will provide proof of concept and feasibility, and hopefully begin the process of generating evidence-based data.

Another key need is identification, prevention, and more effective management. While these are (obviously) quite broad areas to "lump together," solving one or more of these problems would allow for the use of potentially more active combination ICI regimens (e.g. triplets or quadruplets). Prevention or effective rescue agents would "de-risk" the use of these regimens, while identification of patients at risk would allow for treatment stratification with personalized regimens (e.g. low-risk patients receiving the most aggressive triplet or quadruplet, while high-risk patients receive anti-PD-1 combined with chemotherapy).

The microbiome will also play a large and growing role in ICI treatments. Fecal microbial transplants have already demonstrated proof of concept to restore colonic health in refractory colitis patients and, more tantalizingly, convert patients with non-responding melanoma tumors into durable responses. Unlocking the key bacterial species and more effectively harnessing the microbiome will likely play a large role both in enhancing efficacy and toxicity concerns from ICI therapy.

How will this field evolve in the future? While acknowledging that predictions are extremely inaccurate, I would posit that the field will change in the following ways. In the near term, the development of an early evidence base will reduce treatment related mortality and potentially enable more aggressive ICI regimens. Several studies will likely demonstrate utility for rescue agents (e.g. abatacept or tocilizumab), thereby further reducing irAE-related deaths. Biomarker studies may identify some candidates, but the apparent stochastic nature of irAEs will generally continue to stymie prediction efforts on an individual patient level. Increased interest into the long-term effects of ICI will also grow, with large-scale efforts undertaken to characterize the effects of ICI on other immune-mediated processes such as atherosclerosis and neuro-inflammation. In the longer term, it is impossible not to be bullish on artificial intelligence as a potential enabler of irAE prediction and more effective personalized use of cancer treatment in many arenas. Artificial intelligence may enable untangling of multiple potentially confounding variables such as host and tumor genetics, microbiome, and clinical factors [122].

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Article highlights

- The development of irAEs is a frequently encountered, off-target effect of treatment with immune checkpoint blockade that can occur at variable timepoints, necessitating careful monitoring in all patients receiving ICIs.
- IrAEs affect virtually any organ system and current management, monitoring, and risk of severe toxicities is dependent upon therapies received, organs affected, and insights into potential biomarkers.
- Increased understanding of inflammatory processes leading to irAEs has informed current and promising treatment strategies to address steroid-refractory toxicities.

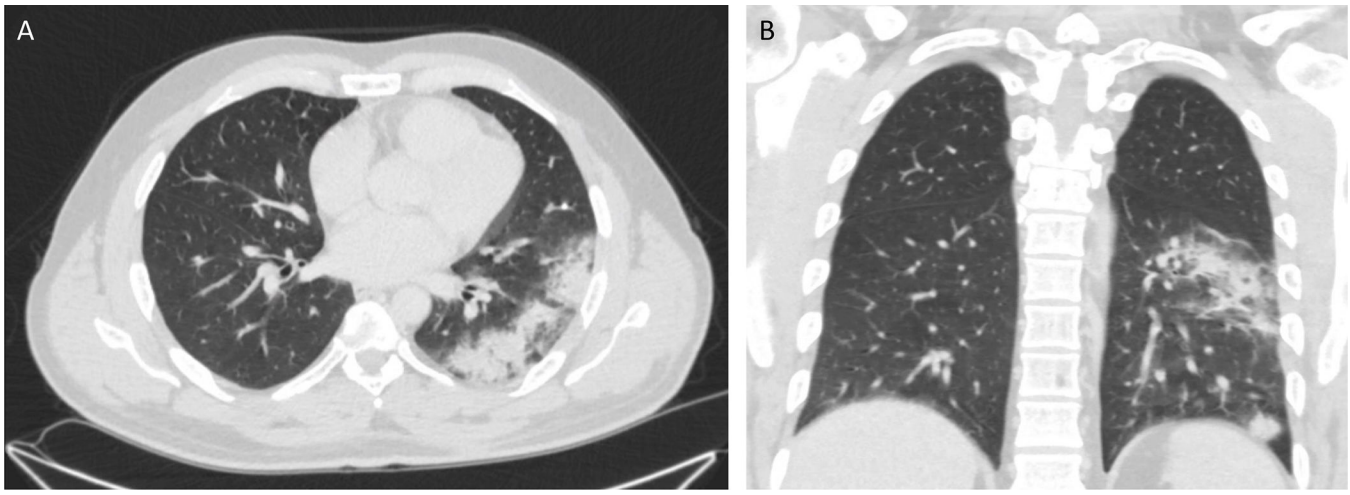

Figure 1.

Pembrolizumab-Induced Pneumonitis in a Patient with Melanoma

CT chest with contrast demonstrating left lower lobe consolidation and surrounding ground glass opacity. A. Axial view. B. Coronal view.

Table 1.

Therapies for Steroid-Refractory Toxicities

Toxicity Type	Therapies Considered if Steroid-Refractory
Cutaneous	phototherapy, omalizumab, dupilumab, acitretin, methotrexate, apremilast, IVIG, rituximab, cyclosporine, anti-TNF
Colitis	infliximab, vedolizumab, fecal microbiota transplant
Hepatitis	azathioprine, MMF, tacrolimus, anti-thymocyte globulin
Pneumonitis	MMF, cyclophosphamide, IVIG, infliximab, tocilizumab
Rheumatologic	methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, anti-TNF, anti-IL-6
Myocarditis	MMF, tacrolimus, anti-thymocyte globulin, abatacept, belatacept, alemtuzumab
Nephritis	infliximab, MMF, azathioprine, cyclophosphamide
Neurologic	IVIG, plasmapheresis, rituximab
Hematologic	rituximab, cyclosporine, IVIG, MMF, anti-thymocyte globulin, tocilizumab, etoposide

MMF = mycophenolate mofetil, IVIG = intravenous immunoglobulin, TNF = tumor necrosis factor, IL-6 = interleukin 6