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Chronic immune-related adverse events arising from immune checkpoint inhibitors: an update

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment, improving outcomes for many patients. However, toxicities termed immune-related adverse events (irAEs) are limitations of these revolutionary treatments. These irAEs may resolve with treatment or ICI cessation (acute) or persist many months beyond therapy cessation (chronic). Acute irAEs were the first to be recognized and are thus more well studied. However, chronic irAEs have been highlighted in recent years and are becoming a topic of more intensive investigation. These chronic irAEs have been noted to affect many different organ systems, including endocrine, rheumatologic, gastrointestinal, dermatologic, neurologic, and cardiovascular systems. In this review, we discuss current knowledge surrounding the frequency, time course, and risk factors associated with chronic irAEs affecting various organ systems, treatment approaches, and future directions.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are now approved for at least 17 different cancer types, and have resulted in increased patient survival.[1] As of March 2020, an estimated 38.5% of patients are eligible to receive ICIs and more than 230,000 patients had been treated at that time.[2] The recent Food and Drug Administration (FDA) approval of relatlimab brings to the total of FDA-approved agents to 10, and a number of eligible patients for ICI therapy continues to rise.[3 4] With improved survival due to durable responses, and the use of therapy in earlier stages of disease, the importance of studying long-term outcomes has increased.

There are three main targets of currently approved ICIs: cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1), and lymphocyte activating gene 3 (LAG3), all negative regulators of T-cell function. Cancer cells can hijack these mechanisms to evade immune recognition and clearance. CTLA-4 is an inhibitory receptor constitutively found on T cells that decreases T-cell function.[1] Blockade of this inhibitor allows for antigen co-stimulation and broad T-cell activation.[5] The CTLA-4 inhibitor ipilimumab was the first ICI approved, although it has limited single-agent activity in most cancers and is largely used in combination PD-1/PD-L1 blockade. PD-1 is also an inhibitory receptor found on T cells, and causes T-cell exhaustion when bound to its ligand, PD-L1 (expressed on tumor cells or various immune cell subsets, particularly at sites of inflammation).[1] Blockade of this interaction produces potent antineoplastic immune responses, particularly in tumors already infiltrated by tumor-specific T cells.[5] LAG-3 is also a cell surface molecule that negatively regulates T-cell proliferation.[6 7] The LAG3 inhibitor relatlimab is FDA approved for melanoma in combination with PD-1 blockade, and clinical trials are underway in other malignancies.[4] ICI may be used alone or in combination with other therapies, such as other ICI agents, chemotherapy, or targeted therapy in various settings, and are being used in (neo) adjuvant or metastatic contexts.

Although these agents lack the toxicities of conventional, cytotoxic chemotherapy agents, they are not without their side effects, termed immune-related adverse events (irAEs). In murine models, CTLA-4 inhibition results in almost immediate postnatal death due to overwhelming autoimmunity.[8–10] In contrast, loss of PD-1 or PD-L1 function results in less severe toxicities, including a spectrum of model-specific effects, ranging from arthritis to cardiomyopathy.[11 12] LAG3 deletion or blockade worsens type I diabetes in mice,[13] and dual deficiency of PD-1 and LAG3 cause lethal autoimmune myocarditis.[6] However, LAG3 deficiency alone does not seem to cause autoimmunity in some models.[14] Notably, one mouse model has minimal toxicities with deletion of the gene encoding PD-1, or heterozygous deletion of the CTLA-4 encoding gene; however, if these are deleted concurrently, >50% develop fulminant myocarditis.[15]

The toxicity profiles of these agents have somewhat similar patterns in patients, with greater, dose-dependent toxicity resulting from CTLA-4 inhibitors, and increased toxicity observed when ICI are used concurrently (eg, high-grade toxicities in 16%, 27%, and 55% of patients treated with nivolumab, ipilimumab, and the combination, respectively).[16–19] PD-1/PD-L1 blockade produces high-grade toxicities in 10–20% of treated patients, and these do not appear dose-dependent at clinically relevant doses.[20] LAG-3/PD-1 blockade in combination produces modestly increased toxicities; high-grade adverse events were observed in 18.9% of patients (compared with 9.7% for nivolumab alone).[4]

Most early studies primarily focused on acute toxicities, which tend to improve or resolve with corticosteroids. However, it was quite apparent even from early studies that the endocrine system was prone to developing chronic toxicities. With thyroid, pituitary, adrenal, or beta-islet cell inflammation, the hormone-producing cells usually do not recover from the T cell-induced inflammation, resulting in long-term hormone deficiency. However, it has become increasingly clear that long-term toxicities occur with a broader range beyond endocrinopathies. While chronic toxicities are less common and clinically obvious than acute toxicities in many cases, they remain an important source of morbidity. One definition proposed by our group defined chronic toxicities as those lasting >3 months after ICI discontinuation. A study by our group suggested that chronic irAEs may occur in as many as 43.2% of patients treated with anti-PD-1 in the adjuvant setting.[21]

Herein, we will explore the pathophysiology of chronic irAEs, their relevance to different organ systems, treatment approaches, and briefly discuss other long-term complications of ICI.

PATHOPHYSIOLOGY

Previous studies have demonstrated the possibility of long-lasting responses to ICI.[22 23] However, predicting which patients will benefit, and for how long remains challenging. Interestingly, patients who experience this long-term benefit have expanded T and B cells that cultivate memory.[24 25] Additionally, studies have demonstrated a correlation between toxicity and patient survival/benefit, generally showing improved survival for patients with some degree of toxicities.[26–28] Although these data could be suggestive of an interlinked relationship between antitumor activity and toxicity, the existence of such a relationship, or the mechanistic basis thereof, remains uncertain.

The mechanisms of chronic irAEs are not well understood.[29] At an organ-specific level, there are two different hypothetical causes of irAE sequelae: burnout or smoldering inflammation. Burnout refers to irreversible damage caused by inflammation, resulting in organ injury and/or dysfunction. One example of this includes endocrinopathies: the hormone-producing cells are destroyed with ensuing and persistent hypofunction. Neuropathy may be another example, with T-cell mediated damage to peripheral nerves causing persistent pain or numbness. In contrast, smoldering inflammatory toxicities appear caused by persistent inflammation that may or may not resolve with time. ICI-induced arthritis may represent such a phenotype, with persistent, ongoing joint inflammation; the initial synovial damage could also contribute to persistent pain and other symptoms.

Other mechanistic considerations are only beginning to be elucidated. It remains poorly understood why some patients experience chronic (or even acute) toxicities whereas others are unaffected. This may be related to cross-reactivity between tumor and self-antigens,[30] environmental exposures,[31] microbiome composition,[32] smoldering autoimmunity,[33] tissue-resident immune cells,[34] genetic predisposition,[35] or some combination of these factors.[36] Similarly, understanding why some toxicities evolve into a chronic phenotype while others resolve remains challenging.

Additionally, it appears that the type of ICI blockade does not obviously impact likelihood of chronicity. At 6.5 years follow-up for the CheckMate 067 trial, time to onset and resolution for treatment-related adverse events were reported for ipilimumab versus nivolumab versus ipilimumab/nivolumab.[37] There did not appear to be an obvious difference for median time to resolution, range of resolution time, or per cent resolved between these three groups. Given the recent approval of LAG3 inhibitors, long-term data is not available. In RELATIVITY-047 trial, median follow-up was 13.2 months, and per cent of patients with persistence was not reported.[4]

ORGAN SYSTEMS

The incidence of chronic irAEs is difficult to quantify, given the complex course of many patients with metastatic cancer. Many patients either die of their disease in a short time frame after treatment, or transition to additional systemic or regional therapies (eg, surgery or radiation) with their own toxicities, thus limiting the ability to reliably follow symptoms over extended periods or attribute them to a specific therapy.

One retrospective study attempted to circumvent these limitations by focusing on patients who received adjuvant therapy, who have lower incidence of cancer deaths or subsequent therapies.[21] This study reported a demonstrated a chronic irAE incidence of 43.2%; only 14.4% of these had resolved with a median follow-up of 529 days. Most chronic irAEs in this study were mild (96.4% grade 1–2).[21] However, this study did not identify an association between age, gender, nor time of onset and development of chronic irAE.[21] Extended follow-up from this study showed an increase in resolution rate after a minimum follow-up of 18 months (35.4%), including 50% resolution of non-endocrine toxicities.[38] Conversely, this means up to 27% of patients experience irAEs which persist more than 18 months beyond treatment cessation (including

half with endocrine and half with non-endocrine toxicities), thus highlighting the long-term impact of chronic irAEs.

An additional systematic review assessed 323 patients with chronic non-endocrine irAEs from 228 studies, largely case reports (n=184) but also including retrospective and prospective cohorts. This study found that 52% of the chronic irAEs persisted more than 6 months, with median symptom duration of 180 days.[39] Approximately equal numbers were grade 1–2 (44.3%) versus grade 3–4 (55.7%), and the most common systems impacted were rheumatologic (20%), neurologic (19%), gastrointestinal (16%), dermatologic (14%), and hematologic (12%). Approximately 16% of patients were on steroids at last follow-up, with a median steroid duration of 120 days. Of note, the preponderance of case reports in this systematic review suggests that these chronic irAEs may be more severe than chronic irAEs in an unselected population.

Different organ systems appeared to have distinct risk of transformation to chronicity (table 1). In our retrospective series, organs with low environmental exposure had lower rates of development (eg, liver, brain, kidneys, heart) while endocrine organs and organs with high environmental exposure (skin, lungs, colon) had higher rates of development.[21] Organs with exposure to environmental antigens could potentially contribute to ongoing antigen

Table 1 Rates of transformation from acute to chronic immune-related adverse event

Toxicity type	Acute and delayed incidence (% of total patients)	Chronic incidence (% of patients with acute/delayed toxicity)	Persistent at 1.5 years follow-up (% of patients with chronic toxicity)
Cutaneous	**110 (34.6)**	**30 (27.3)**	**13 (43.3)**
Dermatitis/pruritus	95 (29.9)	21 (22.1)	9 (40.9)
Psoriasis	4 (1.3)	1 (25)	None
Vitiligo	8 (2.5)	6 (75)	4 (66.7)
Other	3 (0.9)	2 (66.7)	None
Endocrine	**77 (24.2)**	**64 (83.1)**	**54 (84.4)**
Adrenal insufficiency	10 (3.1)	8 (80)	8 (100)
Diabetic ketoacidosis	1 (0.3)	0	None
Hypophysitis	8 (2.5)	8 (100)	8 (100)
Other	1 (0.3)	0	None
Thyroiditis/hypothyrodism	56 (17.6)	48 (85.7)	38 (79.2)
Gastrointestinal	**79 (24.8)**	**13 (16.5)**	**3 (23.1)**
Colitis/diarrhea	40 (12.6)	5 (12.5)	3 (60)
Esophagitis/gastritis/enteritis	7 (2.2)	3 (42.8)	None
Hepatitis	22 (6.9)	4 (18.2)	None
Mucositis	5 (1.6)	2 (40)	None
Other	5 (1.5)	1 (20)	None
Neurological	**16 (5.0)**	**12 (75)**	**7 (58.3)**
Neuropathy	7 (2.2)	6 (85.7)	4 (66.7)
Other neurotoxicity	9 (2.8)	6 (66.7)	3 (50)
Pulmonary	**20 (6.3)**	**10 (50)**	
Cough	2 (0.6)	2 (100)	None
Pneumonitis	18 (5.6)	8 (44.4)	3 (37.5)
Rheumatologic	**80 (25.2)**	**37 (46.3)**	**24 (64.9)**
Arthritis/arthralgias	53 (16.7)	26 (49.1)	18
Myalgias	6 (1.9)	0	None
Other	3 (0.9)	1 (33)	None
Xerostomia	18 (5.6)	10 (55.6)	6 (60)
Other			
Hematologic toxic effects	3 (0.9)	0	Not noted
Nephritis/nephrotic syndrome	5 (1.6)	4 (80)	2 (50)
Ocular toxic effects	7 (2.2)	4 (57.1)	2 (50)

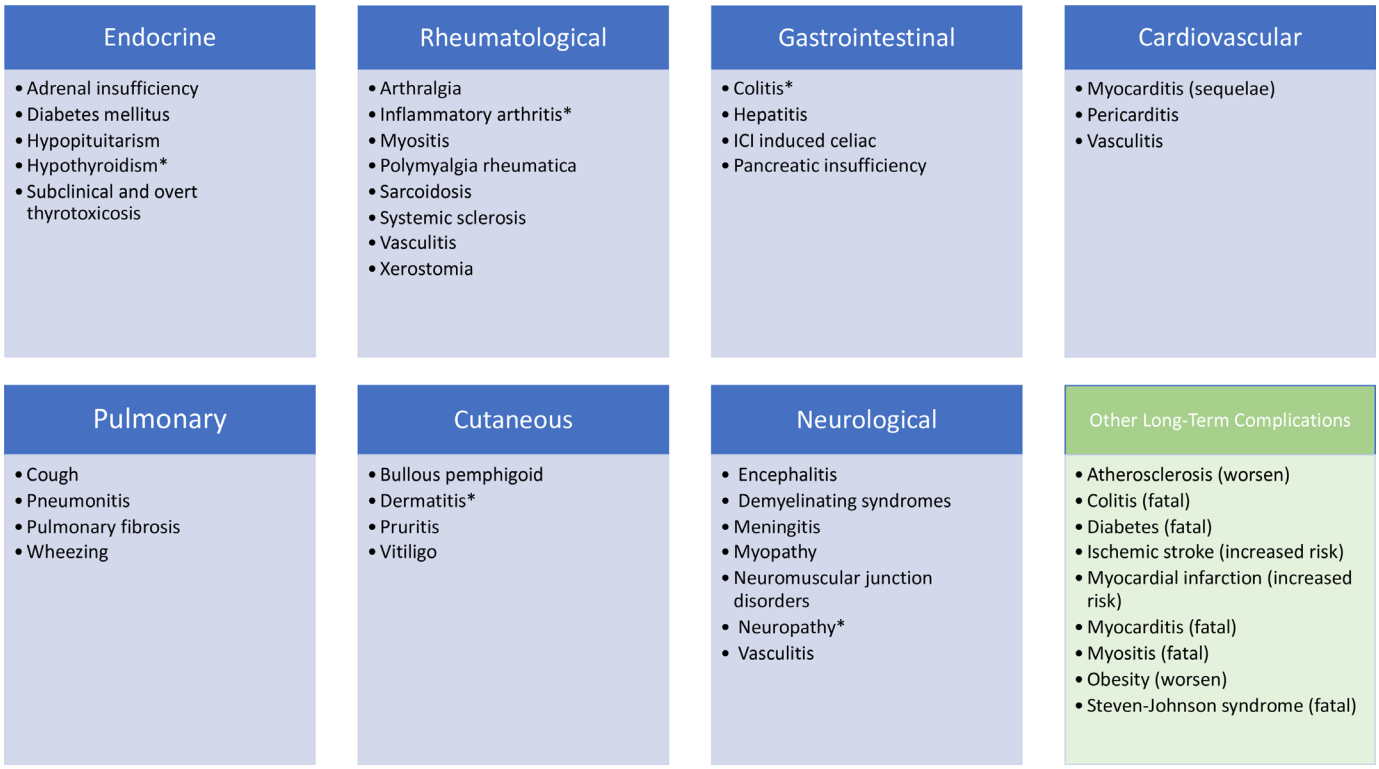

Figure 1 Documented chronic irAEs in each organ system (blue) and possible complications (green). Asterisk denotes the most common chronic irAE in each organ system. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

exposure and inflammation, while endocrine organs have unique susceptibility to total destruction of hormone-producing cells. Meanwhile, organs with less exposure to the outside world therefore have less immune reactivity, as well as (in some cases) more functional redundancy. Additionally, organs that are truly immune privileged (testicles, brain) may experience irAEs, but appear to occur at much lower rates. Documented chronic irAE types may be viewed in figure 1. Importantly, it is not yet determined if the development of chronic irAEs correlate with ICI response.

Table 1 is adapted from Goodman *et al*.[38] Because different cancers have different long-term survival and different regimens used, it is very difficult to untangle whether different cancers confer different risks of chronic irAEs, and whether tumor biology affects the likelihood of chronicity; this is an underexplored area of research. In fact, it has been difficult to even make this association for acute toxicities, other than for a few exceptions (eg, vitiligo and melanoma, pneumonitis and lung cancer).[40 41] The field is even less developed in the realm of chronic toxicities.

Endocrine

Endocrine irAEs are known to have the highest rates of chronicity, with 83% of acute endocrinopathies developing into a chronic phenotype (in one series, 73 of 88 cases).[21] Endocrinopathies arise at a median of 6 weeks into treatment, although may arise at any point during, or up to 1 year after treatment.

Within the endocrine system, hypothyroidism is the most common irAE (10.6% of patients treated with anti-PD-1 monotherapy), and is preceded by a transient thyrotoxicosis in approximately half of cases.[42] The presence of anti-thyroid antibodies predicts the onset of hypothyroidism, although are not routinely ordered clinically.[33] In published literature and in our experience, hypothyroidism resolves only in extraordinarily rare cases; steroids do not appear effective in preventing the onset of hypothyroidism.[40 41] In contrast, subclinical thyrotoxicosis and, less often, overt thyrotoxicosis may resolve and not develop into overt hypothyroidism.[43] Treatment is similar to non-ICI-related hypothyroid, and involves levothyroxine supplementation with regular monitoring of thyroid function levels.

Hypopituitarism (with or without hypophysitis) occurs most often with combination ipilimumab and nivolumab (with up to 10% incidence),[19 44] and initially appeared to be much more rare with anti-PD-1 monotherapy (<1%). Subsequent studies in the adjuvant setting, however, have suggested that chronic hypopituitarism and/or adrenal insufficiency occur in approximately 2–3% in patients treated with anti-PD-1 monotherapy.[21 45] Although most cases of hypophysitis result in secondary adrenal dysfunction, up to 20% of cases do not impact adrenal function, and another 20–25% do not cause secondary thyroid dysfunction. Approximately half of the cases also involve gonadal dysfunction, which is likely underdiagnosed clinically.[43 44] Insulin-dependent diabetes has been documented almost exclusively in patients receiving anti-PD-1

containing regimens.[46] Diabetes and hypopituitarism are extremely important to recognize as they can be highly morbid or fatal if not properly recognized and treated. Both conditions usually do not resolve and are treated with appropriate hormone replacement. Endocrine referral is generally indicated in both conditions.

Rheumatological

Following endocrinopathies, rheumatological irAEs have been recognized as the next most common chronic irAE, with chronicity developing in 20% of affected patients.[39] Rheumatological irAEs have a heterogeneous presentation including inflammatory arthritis, arthralgia, xerostomia, polymyalgia rheumatica, myositis, sarcoidosis, vasculitis, and systemic sclerosis.[47 48]

Arthritis was noted as the most common, comprising 55% of rheumatologic chronic events. In one study, 53.3% of patients with inflammatory arthritis (IA) had persistent symptoms at last follow-up (median follow-up 9 months) without resolution. Interestingly, this persistence was correlated with better treatment response, although time-dependent follow-up may confound these types of associations.[49] Length of ICI treatment was also correlated with persistence of IA. Additionally, in one case presentation, a nivolumab-treated patient with grade 3 chronic polyarthritis demonstrated blockage of the PD-1 receptor in synovial tissue even 200 days past treatment cessation.[50] This may hint at a possible pathophysiology for persistent ICI-induced arthritis. Xerostomia was noted in one study to have a prevalence of 2.3%; in our experience this toxicity often slowly improves over a period of months to years.

Management of chronic arthritis is not well defined, but generally mirrors treatment of other IA syndromes, including non-steroidal anti-inflammatories, low-dose steroids, and disease modifying anti-rheumatic drugs (DMARDs). Although not meeting the definition of a "chronic toxicity", some patients who have ongoing IA and need for continued ICI treatment may be managed with concurrent low-dose prednisone or other agents (eg, hydroxychloroquine or methotrexate). Rheumatology co-management is often indicated in such cases.

Of note, patients with existing rheumatological autoimmune diseases are at increased risk of developing toxicities related to their underlying rheumatological illness.[51] However, the risk factors for the development of chronic rheumatological irAE are not known.

Gastrointestinal

Documented chronic gastrointestinal (GI) irAEs include colitis, ICI-induced celiac disease, hepatitis, and pancreatic insufficiency.[52] Colitis is the most common GI toxicity, but overall has low rates of becoming a chronic process (6 out of 44 acute cases in our series).[21 53] In our experience, patients with chronic colitis tend to ultimately resolve, although some patients do have symptoms that last for multiple months after therapy discontinuation, and/or require prolonged steroids or other biologics. Similarly, hepatitis, which may also flare on or after steroid taper, tends to ultimately resolve with steroids or mycophenolate, and has a very low rate of long-term persistence.[54] Among patients with chronic diarrhea with concern for colitis (particularly if non-responsive to steroids), patients should have a workup to rule out other entities, including pancreatic insufficiency, celiac disease, or microscopic colitis. It is known that ulcerative colitis and Crohn's disease increase the risk of colon cancer; however, it is not known if ICI-induced colitis will have a similar effect. One study did show an association between ICI-induced colitis and increased polyp incidence.[55] Acute pancreatitis, which may be subclinical, may trigger pancreatic insufficiency; one series suggested that pancreatic atrophy occurs in up to 8% of patients treated with anti-PD-1 (the vast majority of which did not have overt pancreatitis), although the clinical significance of this finding is not clear.[56]

Cardiovascular

Myocarditis, although rare, may present in fulminant fashion and has the highest fatality rate among irAEs, largely due to progressive arrhythmias or concurrent skeletal/diaphragmatic muscle involvement.[57 58] Surviving patients may have significant sequelae of critical illness, although the risk of a persistent inflammatory cardiomyositis is not clear; similarly the incidence of subsequent cardiomyopathy is not well defined. Pericarditis and vasculitis have also been associated with ICI therapy. Chronic cardiac toxicities are rare overall, constituting only 2% of non-endocrine chronic irAEs.[39] Of note, thymic size has been suggested as a biomarker of (cardio)myotoxicity, though will need additional validation.[59]

ICI use has been correlated with increased risk of myocardial infarction, ischemic stroke, and coronary intervention in some studies.[60] Preclinical studies have suggested that PD-1/L-1 blockade accelerates atherosclerosis via T-cell activation, which could explain the mechanism of this finding.[61] Accordingly, at least one study noted an expansion in atherosclerotic plaque volume, although another study showed stable to decreased calcified plaque volume.[54 56 62] Another study suggested that combination PD-1/CTLA-4 blockade (but not monotherapy) was associated with increased systolic blood pressure.[63] The long-term effects of ICI therapy on cardiovascular function and outcomes remain an important clinical question.

Pulmonary

Potential chronic pulmonary irAEs include pneumonitis, pulmonary fibrosis, and wheezing or cough.[52] Although the large majority of pneumonitis cases improve with steroids, steroid-refractory disease has a high fatality rate (up to 2/3 in one series).[64] Chronic sequelae may be related to scarring caused by the initial inflammation; progressive fibrosis similar to idiopathic pulmonary fibrosis, however, appears extremely rare. However, in one study, 4 of 23 patients with pneumonitis had persistent symptoms at >1 year; with the majority of patients

retaining persistent imaging abnormality ranging from ground glass to fibrotic appearing changes.[65] However, it is uncertain what, if any effects the persistent imaging findings may have. Potentially, these patients could have a subtler but still important decrease in exercise capacity.[65] Sarcoidosis may occur, but generally resolves on its own or with steroids.

Cutaneous

Chronic cutaneous toxicities may include pruritus, dermatitis, vitiligo, and bullous pemphigoid, and comprise 15–20% of chronic toxicities.[38 66] While dermatitis and pruritus generally resolve with treatment discontinuation and/or immunomodulation, the specifics of treatment and resolution time have not been documented. Additionally, the prevalence and resolution time of other types of chronic cutaneous toxicities have not been studied as well. Importantly, one study showed that dermatology examination of the patient was associated with increased survival.[67] Dermatology co-management may allow for effective management of the irAE with ICI continuation.

One study detailed the presentations of chronic irAEs, with 11% of cutaneous patients diagnosed with dermatitis, 11% with vitiligo, and 20% with bullous pemphigoid.[39] Interestingly, one small case series showed that ICI-induced bullous pemphigoid often persisted for months despite discontinuation, while bullous pemphigoid caused by other agents typically resolved after discontinuation.[68] This longer lasting symptomatology may also signal a more persistent pharmacodynamic effect of ICI treatment. To support this, all three patients in the case series had either continued response or stable disease.

Vitiligo, which is nearly always chronic, is more common in patients with melanoma treated with ICI than in other cancer types.[52] Importantly, development of vitiligo is associated with improved antitumor response.[69] Other reactions (morbilliform, lichenoid, eczematous, immunobullous) may also have an improved prognosis, although these associations appear less robust.[61 63 64] Studies have suggested that chronic cutaneous irAEs are also associated with improved survival, although again time-dependent bias may confound these types of analyses.[70 71] Finally, Steven Johnson syndrome, while generally acute in presentation, is potentially life threatening and requires prompt treatment discontinuation.[72]

The treatment of cutaneous toxicities depends on the underlying diagnosis, and dermatology referral or biopsy can be instrumental. For example, dermatitis may be treated with topical or less often oral steroids; bullous pemphigoid may necessitate biologic therapy. Overall, though, treatment of chronic skin-related irAEs is largely similar to that of their classical autoimmune counterparts.

Neurologic

Neurologic irAEs are broadly classified as meningitis/encephalitis, demyelinating syndromes, vasculitis, neuropathy, neuromuscular junction disorders, and myopathy.[73] They tend to occur within 6 months of treatment initiation, but can develop at any point during treatment, and are more common in ipilimumab-containing regimens.[66 67] Neurotoxicities were some of the most common irAEs to have chronic sequelae (11 out of 15 in one series),[21] and may also have a higher fatality rate than many other irAEs, particularly encephalitis, Guillain Barre, and myasthenia gravis.[73]

Chronic complications from neurologic irAEs may relate more to the initial damage incurred rather than persistent inflammation. Neuropathy appears to be the most common chronic neurologic irAE, likely reflecting T-cell mediated damage to peripheral nerves, although some cases completely resolve. Other neurotoxicities became chronic in small numbers: 2 Guillain-Barré syndrome (18%), 1 Bell palsy (9%), 1 parkinsonian gait (9%), 1 myasthenia gravis (9%), 1 autonomic neuropathy (9%), 1 tremors (9%), and 1 transverse myelitis (9%).[21] A systematic review also reported chronic neurologic irAEs, including myasthenia gravis (25% of chronic neurologic irAEs) and encephalitis (13%), peripheral neuropathy (12%), polyradiculoneuropathy (5%) and polyneuropathy (3%).[39] Myenteric neuropathy resulting in ileus or gastrointestinal dysfunction may also occur rarely, and may not be reversible in some cases.[68 69 74 75] While meningoencephalitis typically does not evolve into a long-term inflammatory condition, myasthenia gravis can progress into a chronic process analogous to non-ICI-associated myasthenia.[76] Guillain-Barre, if not fatal, often causes residual weakness.[77] Pre-existing neurological disorders are also a consideration when starting ICI; ICI may fatally worsen the existing condition, although the frequency and severity of these flares is not well defined. If these patients are treated with ICI therapy, neurology co-management is highly encouraged.[73]

Other systems

Ocular irAEs, primarily uveitis, may become chronic in about some cases; four out of seven ocular toxicities became chronic (57.1%) in one series.[21] Nephritis tends to be steroid-responsive,[78] but frequently produces chronic kidney disease with partial renal recovery (in up to half of cases) and rarely end-stage renal disease requiring hemodialysis.[79] Hematologic toxicities may cause acute morbidity, but may also produce a more chronic phenotype analogous to their non-ICI-induced counterparts (eg, hemolytic anemia, aplastic anemia, or immune thrombocytopenic purpura).[80–82]

TREATMENT APPROACHES

A number of guidelines exist for the management of irAEs, though these largely focus on the management of acute irAEs.[83 84] Thus, standardized management of non-endocrine chronic irAEs remains poorly defined.

Although treatment is often specific to the organ involved, there are several general principles that can be considered. Reduction of steroid use to the lowest possible dose in patients with non-resolving, symptomatic

toxicities should be done. Steroid-sparing agents, particularly agents without substantial effects on T-cell function should be considered when appropriate. Other adjunctive agents for supportive care and symptom control should also be optimized. Referral to appropriate specialists with organ-specific expertize may also help improve patient outcomes. Consideration of weaning steroids or other adjunctive therapies may also be considered periodically, as in our experience many toxicities do improve over a period of months to years. For example, a patient with arthritis may ultimately be able to be weaned off steroids over time.

The treatment of endocrine toxicities generally comprises a separate category, as they nearly always evolve into a chronic phenotype, and do not require high doses of steroids. Rather, the standard of care is hormone replacement and continuation of ICI. However, a systematic study has not been performed to wean patents off replacement therapy and gage for persistence of endocrinopathy. Additionally, whether there is ongoing inflammation in the gland is not certain. For example, for hypophysitis, pain tends to get improve with steroid administration, and patients achieve long-term stability with hormone replacement. Yet, in one case report, hypophysitis flared with ICI rechallenge.[85] As noted, endocrine co-management is generally recommended, particularly for oncology providers that do not have extensive experience with ICI toxicity management.

For other systemic chronic irAEs, systemic steroids are often the mainstay of treatment. Excluding endocrine irAEs, 76% of patients required systemic steroids for treatment, with a median treatment time of 120 days.[39] Patrinely *et al* suggested that 32.9% of patients required systemic glucocorticoids. However, for rheumatological irAEs, approximately 2/3 of patients required DMARDS for at least some duration.[86]

While systemic steroids offer clear benefit to irAE treatment, there is concern about the impact of long-term steroid use or immunosuppression on cancer outcomes. The toxicities of ICIs may be intricately linked with their efficacy; patients with irAEs generally have improved outcomes compared with those without.[87–89] Given this data, it is possible that either (1) steroids partially blunt antitumor immunity in a dose/timing dependent manner, or (2) steroids have minimal effects on antitumor immunity. The currently available data regarding the topic, however, is not definitive.

Two studies demonstrated worsened outcomes in patients treated with steroids within 2 months of starting ICI treatment,[90 91] while another small study suggested that patients with hypophysitis had better outcomes when treated with low-dose versus high dose steroids.[92] For patients treated for irAEs at any time in their course, another study showed worse outcomes for those with high-dose steroid usage rather than low dose for cancer symptoms, but no obvious association with steroid dose used for irAEs or autoimmune disease.[93 94] However, a different study showed comparable outcomes when comparing patients who did and did not use systemic steroids for irAEs.[95] That data is more scant regarding long-term steroid use. In our experience, patients treated for adrenal insufficiency with steroids, or patients with arthritis treated with low-dose prednisone appear to do well, though larger studies should confirm this. Another study that supports that chronic judicious immunomodulation may not adversely impact antitumor efficacy; a retrospective study assessed patients with colitis that either had ongoing infliximab or vedolizumab along with ICI retreatment, or retreatment alone. This study showed decreased colitis flares and equivalent antitumor outcomes.[96]

Another consideration is rechallenge. Some patients with either acute or chronic irAEs may have indications to consider retreatment with ICI therapy (eg, prolonged initial benefit from therapy with subsequent progression) or escalation to a different class (eg, progression on PD-1 blockade with consideration to escalate to PD-1/CTLA-4 blockade). There are no contraindications to retreatment of patients with endocrinopathies, though in our experience hypophysitis may flare with compressive symptoms (eg, headaches).[85] In one series, 32.4% of patients flared with rechallenge.[38] In our experience, active chronic irAEs may also be managed with ongoing low-dose steroids in the context of rechallenge. Other immunomodulating agents (eg, tumor necrosis factor (TNF)-alpha inhibition or tocilizumab) given concurrently with rechallenge might be an option for more severe irAEs.

Prophylaxis of chronic irAEs is another area of interest. In theory, preventing acute irAEs should in turn prevent chronic irAEs. Recent studies have demonstrated promise for infliximab and vedolizumab as preventative treatment for specific irAEs.[96] Unfortunately, prophylaxis of irAEs has otherwise not been well studied. However, biomarkers to predict irAEs is an area of new study. For example, colonization of the gut microbiome may enhance antitumor response, and certain human leukocyte antigen (HLA) genotypes have been connected to greater risk of irAE development[97]; microbiome modulation is thus a potential method for irAE prevention.

OTHER LONG-TERM COMPLICATIONS

As noted, irAEs may result in fatalities, particularly severe events include myocarditis, pneumonitis, Steven Johnson syndrome, diabetes, colitis, myasthenia gravis, and myositis. These most often occur early in treatment. Fatal events depend on the regimen received, with CTLA-4 deaths most often from colitis and anti PD-1 deaths most often from pneumonitis.[98] Rates of fatalities were approximately 0.4% from single-agent PD-1/PD-L1 blockade, and up to 1.2% for combination PD-1/CTLA-4 inhibition.

Aberrant immune cell activation contributes to many pathologic processes. Notably, preclinical data has raised the concern that ICI may worsen atherosclerosis. In mice, removal of PD-1/PD-L1 led to increased T cell and macrophage infiltration into atherosclerotic plaques

and increased atherosclerotic burden.[99 100] In obesity, T cells play an important function, and the T-cell activation by ICI may theoretically worsen obesity.[101 102] Currently, evidence for the long-term impact of ICI on these processes remain mixed. Several cohort studies have not shown obvious increases in weight or other unfavorable metabolic changes.[42] However, others have suggested increased cardiovascular events.[103] Other impacts, such as long-term microbiome changes, impact on aging, and neurologic impacts have not been quantified.

CONCLUSIONS AND FUTURE DIRECTIONS

Chronic irAEs can affect many different organ systems, including endocrine, gastrointestinal, dermatologic, rheumatologic, and neurologic. While they have been increasingly highlighted in recent years, more studies are needed to better understand their pathogenesis, outcomes, risk factors, and treatment options. These complications have grown in relevance given the improved outcomes for patients treated with ICI therapy.

Chronic irAEs and other events with long-term implications (eg, fatal toxicities) should be considered by clinicians when making treatment decisions. While in the context of metastatic disease (and many patients receiving treatment in the adjuvant setting), the possibility of transformative benefit from ICI therapy likely outweighs the risks. However, for a subset of patients with low-risk disease (eg, patients with resected IIIA melanoma), or patients treated with combination regimens where the ICI addition may only benefit a subset of patients (eg, neoadjuvant therapy in triple-negative breast cancer), the modest improvement in outcomes could be outweighed by toxicity concerns, particularly those with lifelong implications.

Future directions include addressing many important unmet needs. First, definitions of chronic irAEs should be established. The definition of symptoms persisting at least 3 months after discontinuation is useful, but may be further refined to include whether patients are requiring steroids, and whether symptoms resolve in other relevant time frames (eg, 6 or 12 months). Second, establishing frequency with different regimens, particularly those used in the (neo)adjuvant setting remains important to counsel patients who are candidates for these therapies. Third, identifying the pathophysiology and potential treatments for persistent events is needed. Fourth, characterizing patients with multisystem involvement, or patients with symptoms not classical for irAEs (eg, fatigue) remains important and understudied. Lastly, identifying biomarkers to determine which patients are at risk for long-term irAEs could inform therapy selection and potentially early intervention.

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REFERENCES

1 Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front Oncol* 2018;8:86.
2 Haslam A, Gill J, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for immune checkpoint inhibitor drugs. *JAMA Netw Open* 2020;3:e200423.
3 Opdualag Approved to Treat Advanced Melanoma - NCI, 2022. Available: https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-opdualag-melanoma-lag-3
4 Tawbi HA, Schadendorf D, Lipson EJ, *et al*. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 2022;386:24–34.
5 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–64.
6 Woo S-R, Turnis ME, Goldberg MV, *et al*. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Research* 2012;72:917–27.
7 Anderson AC, Joller N, Kuchroo VK. Tim-3, and TIGIT co-inhibitory receptors with specialized functions in immune regulation. *Immunity* 2016;44:989–1004: .
8 Saha B, Jaklic B, Harlan DM, *et al*. Toxic shock syndrome toxin-1-induced death is prevented by Ctla4Ig. *J Immunol* 1996;157:3869–75.
9 Tivol EA, Borriello F, Schweitzer AN, *et al*. Loss of CTLA-4 leads to massive Lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* 1995;3:541–7.
10 Waterhouse P, Penninger JM, Timms E, *et al*. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. *Science* 1995;270:985–8.
11 Nishimura H, Nose M, Hiai H, *et al*. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999;11:141–51.
12 Programmed death-1 (PD-1)–deficient mice are extraordinarily sensitive to tuberculosis - PMC, 2023.
13 Bettini M, Szymczak-Workman AL, Forbes K, *et al*. Accelerated autoimmune diabetes in the absence of LAG-3. *J Immunol* 2011;187:3493–8.
14 Maruhashi T, Sugiura D, Okazaki I-M, *et al*. LAG-3: from molecular functions to clinical applications. *J Immunother Cancer* 2020;8:e001014.
15 Wei SC, Meijers WC, Axelrod ML, *et al*. A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention. *Cancer Discov* 2021;11:614–25.
16 Tarhini AA, Lee SJ, Hodi FS, *et al*. Phase III study of adjuvant Ipilimumab (3 or 10 mg/kg) versus high-dose interferon Alfa-2B for resected high-risk melanoma: North American Intergroup E1609. *J Clin Oncol* 2020;38:567–75.
17 Eggermont AMM, Blank CU, Mandala M, *et al*. Longer follow-up CONFIRMS recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. *J Clin Oncol* 2020;38:3925–36.

18 Weber J, Mandala M, Del Vecchio M, *et al*. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017;377:1824–35.
19 Larkin J, Chiarion-Sileni V, Gonzalez R, *et al*. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:23–34.
20 Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
21 Patrinely JR Jr, Johnson R, Lawless AR, *et al*. Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma. *JAMA Oncol* 2021;7:744.
22 Brahmer JR, Drake CG, Wollner I, *et al*. Phase I study of single-agent anti-programmed Death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *JCO* 2010;28:3167–75.
23 Patnaik A, Kang SP, Rasco D, *et al*. Phase I study of Pembrolizumab (MK-3475; anti-PD-1 Monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res* 2015;21:4286–93.
24 Kato T, Kiyotani K, Tomiyama E, *et al*. Peripheral T cell receptor repertoire features predict durable responses to anti-PD-1 inhibitor monotherapy in advanced renal cell carcinoma. *Oncoimmunology* 2021;10:1862948.
25 Spassova I, Ugurel S, Terheyden P, *et al*. Predominance of central memory T cells with high T-cell receptor repertoire diversity is associated with response to PD-1/PD-L1 inhibition in Merkel cell carcinoma. *Clin Cancer Res* 2020;26:2257–67.
26 Eggermont AMM, Kicinski M, Blank CU, *et al*. Association between immune-related adverse events and recurrence-free survival among patients with stage III Melanoma randomized to receive Pembrolizumab or placebo. *JAMA Oncol* 2020;6:519–27.
27 Maher VE, Fernandes LL, Weinstock C, *et al*. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. *J Clin Oncol* 2019;37:2730–7.
28 Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer* 2019;7:306.
29 Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378:158–68.
30 Berner F, Bomze D, Diem S, *et al*. Association of checkpoint inhibitor-induced toxic effects with shared cancer and tissue antigens in non-small cell lung cancer. *JAMA Oncol* 2019;5:1043–7.
31 Johnson DB, McDonnell WJ, Gonzalez-Ericsson PI, *et al*. A case report of clonal EBV-like memory Cd4+ T cell activation in fatal checkpoint inhibitor-induced encephalitis. *Nat Med* 2019;25:1243–50.
32 Andrews MC, Duong CPM, Gopalakrishnan V, *et al*. Gut Microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med* 2021;27:1432–41.
33 Zhou X, Iwama S, Kobayashi T, *et al*. Risk of thyroid dysfunction in PD-1 blockade is stratified by the pattern of Tgab and Tpoab positivity at baseline. *J Clin Endocrinol Metab* 2023;108:e1056–62.
34 Luoma AM, Suo S, Williams HL, *et al*. Molecular pathways of colon inflammation induced by cancer Immunotherapy. *Cell* 2020;182:655–71.
35 Middha P, Thummalapalli R, Betti MJ, *et al*. Polygenic risk score for ulcerative colitis predicts immune checkpoint inhibitor-mediated colitis. *medRxiv* 2023.
36 Goodman RS, Jung S, Balko JM, *et al*. Biomarkers of immune checkpoint inhibitor response and toxicity: challenges and opportunities. *Immunol Rev* 2023;318:157–66.
37 Wolchok JD, Chiarion-Sileni V, Gonzalez R, *et al*. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced Melanoma. *J Clin Oncol* 2022;40:127–37.
38 Goodman RS, Lawless A, Woodford R, *et al*. Extended follow-up of chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk Resected Melanoma. *JAMA Netw Open* 2023;6:e2327145.
39 Barron CC, Stefanova I, Cha Y, *et al*. Chronic immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors: a systematic review. *J Immunother Cancer* 2023;11:e006500.
40 Carbone ML, Capone A, Guercio M, *et al*. Insight into immune profile associated with vitiligo onset and anti-tumoral response in melanoma patients receiving anti-PD-1 immunotherapy. *Front Immunol* 2023;14:1197630.
41 Naidoo J, Wang X, Woo KM, *et al*. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol* 2017;35:709–17.
42 Patrinely JR, Young AC, Quach H, *et al*. Survivorship in immune therapy: assessing toxicities, body composition and health-related quality of life among long-term survivors treated with antibodies to programmed death-1 receptor and its ligand. *Eur J Cancer* 2020;135:211–20.
43 Muir CA, Clifton-Bligh RJ, Long GV, *et al*. Thyroid immune-related adverse events following immune checkpoint inhibitor treatment. *J Clin Endocrinol Metab* 2021;106:e3704–13.
44 Faje A, Reynolds K, Zubiri L, *et al*. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from Ipilimumab-associated hypophysitis. *Eur J Endocrinol* 2019;181:211–9.
45 Brancatella A, Pierotti L, Viola N, *et al*. Steroid treatment in the management of destructive thyrotoxicosis induced by Pd1 blockade. *Eur Thyroid J* 2022;11:e220030.
46 Wright JJ, Salem J-E, Johnson DB, *et al*. Increased reporting of immune checkpoint inhibitor-associated diabetes. *Diabetes Care* 2018;41:e150–1.
47 Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. *Nat Rev Endocrinol* 2021;17:389–99.
48 Tan MH, Iyengar R, Mizokami-Stout K, *et al*. Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. *Clin Diabetes Endocrinol* 2019;5:1.
49 Braaten TJ, Brahmer JR, Forde PM, *et al*. Immune checkpoint inhibitor-induced inflammatory arthritis persists after Immunotherapy cessation. *Ann Rheum Dis* 2020;79:332–8.
50 Murray-Brown W, Wilsdon TD, Weedon H, *et al*. Nivolumab-induced synovitis is characterized by florid t cell infiltration and rapid resolution with synovial biopsy-guided therapy. *J Immunother Cancer* 2020;8:e000281.
51 Wang SJ, Dougan SK, Dougan M. Immune mechanisms of toxicity from checkpoint inhibitors. *Trends Cancer* 2023;9:543–53.
52 Johnson DB, Nebhan CA, Moslehi JJ, *et al*. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022;19:254–67.
53 Cappelli LC, Bingham CO. Spectrum and impact of checkpoint inhibitor-induced irAEs. *Nat Rev Rheumatol* 2021;17:69–70.
54 Patrinely JR, McGuigan B, Chandra S, *et al*. A multicenter characterization of hepatitis associated with immune checkpoint inhibitors. *Oncoimmunology* 2021;10:1875639.
55 Machado AP, Shatila M, De Toni EN, *et al*. Colon adenoma after diagnosis of immune checkpoint inhibitor-mediated colitis. *J Cancer* 2023;14:2686–93.
56 Eshet Y, Baruch EN, Shapira-Frommer R, *et al*. Clinical significance of Pancreatic atrophy induced by immune-checkpoint inhibitors: a case-control study. *Cancer Immunol Res* 2018;6:1453–8.
57 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
58 Moslehi JJ, Salem J-E, Sosman JA, *et al*. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet* 2018;391.
59 Fenioux C, Abbar B, Boussouar S, *et al*. Thymus alterations and susceptibility to immune checkpoint inhibitor myocarditis. *Nat Med* 2023;29:3100–10.
60 Zd D, Rm A, J T, *et al*. Association between immune checkpoint inhibitors with cardiovascular events and Atherosclerotic plaque. *Circulation* 2020;142. Available: https://pubmed.ncbi.nlm.nih.gov/33003973/
61 Gotsman I, Grabie N, Dacosta R, *et al*. Proatherogenic immune responses are regulated by the PD-1/PD-L pathway in mice. *J Clin Invest* 2007;117:2974–82.
62 Turker I, Nair S, Terry JG, *et al*. Immune checkpoint inhibitors' effects on calcified aortic plaques in melanoma survivors: a retrospective cohort study. *JACC CardioOncol* 2023;5:536–8.
63 Turker I, Sharma A, Huang S, *et al*. Combination immune checkpoint inhibitor therapy is associated with increased blood pressure in melanoma patients. *Hypertension* 2023;80:e43–5.
64 Balaji A, Hsu M, Lin CT, *et al*. Steroid-refractory PD-(L)1 Pneumonitis: incidence, clinical features, treatment, and outcomes. *J Immunother Cancer* 2021;9:e001731.
65 Johnson DB, Taylor KB, Cohen JV, *et al*. Anti–PD-1–induced Pneumonitis is associated with persistent imaging abnormalities in melanoma patients. *Cancer Immunol Res* 2019;7:1755–9.
66 Bobircă A, Bobircă F, Ancuta I, *et al*. n.d. Rheumatic immune-related adverse events—a consequence of immune checkpoint inhibitor therapy. *Biology*10:561.

67 Thompson LL, Li EB, Krasnow NA, *et al*. Effect of dermatological consultation on survival in patients with checkpoint inhibitor-associated cutaneous toxicity. *Br J Dermatol* 2021;185:627–35.
68 Naidoo J, Schindler K, Querfeld C, *et al*. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res* 2016;4:383–9.
69 Guida M, Strippoli S, Maule M, *et al*. Immune checkpoint inhibitor associated Vitiligo and its impact on survival in patients with metastatic melanoma: an Italian melanoma Intergroup study. *ESMO Open* 2021;6:100064.
70 Freeman-Keller M, Kim Y, Cronin H, *et al*. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res* 2016;22:886–94.
71 Min Lee CK, Li S, Tran DC, *et al*. Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: a retrospective case-control study. *J Am Acad Dermatol* 2018;79:1047–52.
72 Tattersall IW, Leventhal JS. Cutaneous toxicities of immune checkpoint inhibitors: the role of the dermatologist. *Yale J Biol Med* 2020;93:123–32.
73 Guidon AC, Burton LB, Chwalisz BK, *et al*. Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors. *J Immunother Cancer* 2021;9:e002890.
74 Appelbaum J, Wells D, Hiatt JB, *et al*. Fatal Enteric plexus neuropathy after one dose of Ipilimumab plus Nivolumab: a case report. *J Immunother Cancer* 2018;6:82.
75 Bhatia S, Huber BR, Upton MP, *et al*. Inflammatory enteric neuropathy with severe constipation after ipilimumab treatment for melanoma: a case report. *J Immunother* 2009;32:203–5.
76 Johnson DB, Saranga-Perry V, Lavin PJM, *et al*. Myasthenia gravis induced by ipilimumab in patients with metastatic melanoma. *J Clin Oncol* 2015;33:e122–4.
77 Johnson DB, Manouchehri A, Haugh AM, *et al*. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. *J Immunother Cancer* 2019;7:134.
78 Gupta S, Garcia-Carro C, Prosek JM, *et al*. Shorter versus longer corticosteroid duration and recurrent immune checkpoint inhibitor-associated AKI. *J Immunother Cancer* 2022;10:e005646.
79 Cortazar FB, Kibbelaar ZA, Glezerman IG, *et al*. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. *J Am Soc Nephrol* 2020;31:435–46.
80 Leaf RK, Ferreri C, Rangachari D, *et al*. Clinical and laboratory features of autoimmune hemolytic anemia associated with immune checkpoint inhibitors. *Am J Hematol* 2019;94:563–74.
81 Shiuan E, Beckermann KE, Ozgun A, *et al*. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. *J Immunother Cancer* 2017;5:8.
82 Davis EJ, Salem J-E, Young A, *et al*. Hematologic complications of immune checkpoint inhibitors. *Oncologist* 2019;24:584–8.
83 Brahmer JR, Abu-Sbeih H, Ascierto PA, *et al*. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer* 2021;9:e002435.
84 Brahmer JR, Lacchetti C, Schneider BJ, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *JCO* 2018;36:1714–68.
85 Park BC, Jung S, Wright JJ, *et al*. Recurrence of Hypophysitis after immune Checkpoint inhibitor rechallenge. *Oncologist* 2022;27:e967–9.
86 Roberts J, Ennis D, Hudson M, *et al*. Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. *Autoimmun Rev* 2020;19:102595.
87 Cook S, Samuel V, Meyers DE, *et al*. Immune-related adverse events and survival among patients with metastatic NSCLC treated with immune checkpoint inhibitors. *JAMA Netw Open* 2024;7:e2352302.
88 Indini A, Di Guardo L, Cimminiello C, *et al*. Immune-related adverse events correlate with improved survival in patients undergoing anti-Pd1 immunotherapy for metastatic melanoma. *J Cancer Res Clin Oncol* 2019;145:511–21.
89 Das S, Ciombor KK, Haraldsdottir S, *et al*. Immune-related adverse events and immune checkpoint inhibitor efficacy in patients with gastrointestinal cancer with food and drug administration-approved indications for immunotherapy. *Oncologist* 2020;25:669–79.
90 Maslov DV, Tawagi K, Kc M, *et al*. Timing of steroid initiation and response rates to immune checkpoint inhibitors in metastatic cancer. *J Immunother Cancer* 2021;9:e002261.
91 Bai X, Hu J, Betof Warner A, *et al*. Early use of high-dose glucocorticoid for the management of irAE is associated with poorer survival in patients with advanced Melanoma treated with anti-PD-1 monotherapy. *Clin Cancer Res* 2021;27:5993–6000.
92 Faje AT, Lawrence D, Flaherty K, *et al*. High-dose glucocorticoids for the treatment of Ipilimumab-induced Hypophysitis is associated with reduced survival in patients with melanoma. *Cancer* 2018;124:3706–14.
93 Riudavets M, Mosquera J, Garcia-Campelo R, *et al*. Immune-related adverse events and corticosteroid use for cancer-related symptoms are associated with efficacy in patients with non-small cell lung cancer receiving anti-PD-(L)1 blockade agents. *Front Oncol* 2020;10:1677.
94 Ricciuti B, Dahlberg SE, Adeni A, *et al*. Immune Checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. *J Clin Oncol* 2019;37:1927–34.
95 Horvat TZ, Adel NG, Dang T-O, *et al*. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with Melanoma treated with ipilimumab at memorial sloan kettering cancer center. *J Clin Oncol* 2015;33:3193–8.
96 Badran YR, Zou F, Durbin SM, *et al*. Concurrent immune checkpoint inhibition and selective immunosuppressive therapy in patients with immune-related Enterocolitis. *J Immunother Cancer* 2023;11:e007195.
97 Conroy M, Naidoo J. Immune-related adverse events and the balancing act of immunotherapy. *Nat Commun* 2022;13:392.
98 Wang DY, Salem J-E, Cohen JV, *et al*. Fatal toxic effects associated with immune checkpoint inhibitors. *JAMA Oncol* 2018;4:1721.
99 Grabie N, Gotsman I, DaCosta R, *et al*. Endothelial programmed Death-1 ligand 1 (PD-L1) regulates Cd8+ T-cell mediated injury in the heart. *Circulation* 2007;116:2062–71.
100 Porsche CE, Delproposto JB, Geletka L, *et al*. Obesity results in Adipose tissue T cell exhaustion. *JCI Insight* 2021;6:139793.
101 Breuer DA, Pacheco MC, Washington MK, *et al*. Cd8+ T cells regulate liver injury in obesity-related nonalcoholic fatty liver disease. *Am J Physiol Gastrointest Liver Physiol* 2020;318:G211–24.
102 Park BC, Lee AXT, Ye F, *et al*. Immune checkpoint inhibitors and their impact on liver enzymes and attenuation. *BMC Cancer* 2022;22:998.
103 Drobni ZD, Alvi RM, Taron J, *et al*. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation* 2020;142:2299–311.