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Immune-checkpoint inhibitors: long-term implications of toxicity

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Abstract | The development of immune-checkpoint inhibitors (ICIs) has heralded a new era in cancer treatment, enabling the possibility of long-term survival in patients with metastatic disease, and providing new therapeutic indications in earlier-stage settings. As such, characterizing the long-term implications of receiving ICIs has grown in importance. An abundance of evidence exists describing the acute clinical toxicities of these agents, although chronic effects have not been as well catalogued. Nonetheless, emerging evidence indicates that persistent toxicities might be more common than initially suggested. While generally low-grade, these chronic sequelae can affect the endocrine, rheumatological, pulmonary, neurological and other organ systems. Fatal toxicities also comprise a diverse set of clinical manifestations and can occur in 0.4–1.2% of patients. This risk is a particularly relevant consideration in light of the possibility of long-term survival. Finally, the effects of immune-checkpoint blockade on a diverse range of immune processes, including atherosclerosis, heart failure, neuroinflammation, obesity and hypertension, have not been characterized but remain an important area of research with potential relevance to cancer survivors. In this Review, we describe the current evidence for chronic immune toxicities and the long-term implications of these effects for patients receiving ICIs.

Immune-checkpoint inhibitors (ICIs) have emerged as a core pillar of cancer therapy. Nearly half of all patients with metastatic cancer in economically developed countries are eligible to receive ICIs, with eight approved agents available for 17 different malignancies as of December 2021, with increasing use of these agents seen in several (neo)adjuvant and maintenance settings[1]. ICIs are also often being used in combination regimens, including those involving other classes of ICI, cytotoxic chemotherapy, and biological and/or targeted therapies[2]. Moreover, durable responses are becoming increasingly common, even in the metastatic setting[3]; thus, characterizing the long-term physiological implications of treatment with ICIs is growing in importance.

Immune checkpoints are receptors expressed by immune cells that enable dynamic regulation of immune homeostasis and are particularly relevant to T cell functionality. PD-1 and its primary ligand PD-L1 are expressed on T cells, and on tumour cells and tumour-infiltrating myeloid cells, respectively. Interaction of these two proteins results in T cell exhaustion, a potentially permanent state of dysfunction characterized by reduced or absent effector function (cytotoxicity or cytokine production), lack of response to stimuli, and altered transcriptional and epigenetic states[4,5]. This interaction is exploited by tumour cells to maintain immune tolerance, although it is also used

physiologically to limit the extent of autoimmune inflammation, maintain fetal tolerance during pregnancy and prevent the rejection of transplanted organs. Relative to PD-1 (REFS[6,7]), CTLA4 has a more proximal role in immune activation, engaging with the dendritic cell ligand B7 (also known as CD80) and acting as a higher affinity competitor to CD28, thus limiting the extent of T cell activation at the priming stage. Expression of CTLA4 also probably enhances the function and promotes the expansion of regulatory T (T_{reg}) cells in the tumour microenvironment[8]. A more detailed description of the mechanisms of these various immune checkpoints is provided elsewhere[9,10].

Abrogation of immune-checkpoint signalling has several consequences. Data from preclinical studies demonstrate that genetic ablation of *Ctla4* in mice results in death in early life (typically at 3–4 weeks of age) owing to lymphoproliferation and profound multi-organ autoimmunity[11–13]. By contrast, deletion of *Pd1* or *Pdl1* results in less-severe, background-dependent, model-specific effects ranging from arthritis to cardiomyopathy, which usually occur later in life (from 5 to 30 weeks of age)[14,15]. The clinical experience mimics this pattern, in that CTLA4 inhibition results in a high incidence of dose-dependent toxicities (high-grade toxicities in 38.6% and 57.9% of patients with metastatic melanoma receiving ipilimumab 3 mg/kg or

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Key points

- Immune-checkpoint inhibitors (ICIs) produce durable responses in a growing number of patients with metastatic cancer, and are being used increasingly in (neo)adjuvant settings.
- Although acute toxicities are more common, chronic immune-related adverse events (irAEs) are increasingly recognized, and can affect up to 40% of patients.
- Chronic irAEs are mostly classed as endocrine or rheumatological, but can affect a diverse array of organs.
- Other issues with long-term relevance include fatal irAEs (which can occur in 0.4–1.2% of patients), and rechallenge after severe irAEs.
- ICIs could also affect other immune-mediated processes (such as atherosclerosis or neuroinflammation), although more studies are needed.

10 mg/kg, respectively)[16]. By contrast, PD-1 or PD-L1 blockade causes high-grade adverse events in only 10–15% of patients, with similar incidences seen with different agents and across the range of clinically used doses[17,18]. Patterns of response also vary substantially between classes: CTLA4 inhibition has limited activity as monotherapy outside of melanoma (and is associated with a response rate of only 20% in patients with metastatic melanoma)[19]. By contrast, antibodies targeting PD-1 or PD-L1 have clinical activity in nearly 20 different cancer types, with response rates ranging from 10–30% (in many carcinogen-induced solid tumours, including those of the liver, bladder and kidneys), to 40–50% (in melanoma, microsatellite unstable and/or mismatch repair-deficient cancers and strongly PD-L1[+] non-small-cell lung cancers (NSCLCs)) and to as high as 65–75% (in Hodgkin lymphoma)[20,21]. Combination PD-1 and CTLA4 blockade are also being used in many different types of cancer, and are associated with additive or possibly synergistic responses in several clinical settings. For example, in metastatic melanoma, treatment with the anti-PD-1 antibody nivolumab plus the anti-CTLA4 antibody ipilimumab is associated with a 59% response rate (compared with 43% for nivolumab alone and 15–20% for ipilimumab alone)[22], and in renal cell carcinoma (RCC) approximately 40% (versus ~25% with nivolumab alone and probably minimal activity for ipilimumab monotherapy)[23,24]. This combination is also approved for use in patients with NSCLC, microsatellite instability-high colorectal cancer or hepatocellular carcinoma, in whom CTLA4 inhibition has minimal (or poorly characterized) activity as a monotherapy[25]. Unsurprisingly, concurrent inhibition of these non-redundant immune checkpoints also augments the risk of autoimmune toxicities, resulting in increased incidences of high-grade immune-related adverse events (irAEs)[23,26]. Specifically, nivolumab monotherapy, ipilimumab monotherapy and the combination of ipilimumab plus nivolumab have been shown to lead to high-grade adverse events in 23%, 28% and 59% of patients with advanced-stage melanoma, respectively[27].

A feature that is common to all ICIs (whether they inhibit PD-1, PD-L1 or CTLA4), and largely distinct from many other classes of cancer therapeutic agents, is the potential for long-lasting, possibly indefinite responses, even in patients with metastatic solid tumours (TABLE 1) — and particularly in patients

treated in earlier stages (TABLE 2). Duration of response is heterogeneous among patients, although those with tumours associated with higher baseline response rates (such as melanoma) tend to have longer responses. Of note, treatment might be safely discontinued in some patients who have prolonged excellent responses, although the timing and how best to identify eligible patients remain unclear and the oncological safety of this approach will probably vary between tumour types. For example, patients with NSCLC who have either a response or stable disease after 1 year of nivolumab were randomized to continued therapy or observation: continuous treatment resulted in superior overall survival (OS) compared with therapy discontinuation (median OS not reached versus 32.5 months, HR 0.61)[28]. By contrast, several non-randomized studies have indicated excellent outcomes after treatment discontinuation in patients with metastatic melanoma who have ongoing responses after either 1 or 2 years of therapy, with disease progression rarely observed over the ensuing 2–5 years[29–31].

In patients who ultimately have disease relapse despite an initial clinical response (acquired resistance), several mechanisms of treatment failure have been identified, including upregulation of alternative immune checkpoints, defective antigen presentation, a lack of IFNγ response and T cell exclusion[32–34]. By contrast, patients who have durable responses appear to have broadened peripheral T and B cell repertoires, and seem to develop immunological memory (which might also have implications for broader and longer-term T cell-mediated toxicity)[35,36]. The molecular underpinnings of these responses are not entirely clear; potential mechanisms could include complete immune-mediated cytological eradication, generation of immune memory that forestalls disease recurrence or induction of a protracted 'stalemate' between residual cancer and immune cells[37]. Irrespective of the mechanisms of action, the extended duration of the therapeutic effects of ICIs often far surpasses their pharmacokinetic half-life[38,39]. This persistent pharmacodynamic effect (manifesting clinically as durable responses) also has implications for toxicities. In this Review, we describe the available data and clinical experience to date from patients who have chronic and/or irreversible toxicities from ICIs. We also discuss the clinical implications of these effects, including their relevance to treatment decision making, and their long-term implications for other inflammatory processes (TABLE 2).

Immune activation and irAEs

The immune activation that underlies most irAEs might be coupled with the activity required for antitumour immune responses (FIG. 1). This tumour-specific hypothesis is supported by the modest but reproducible positive correlation between therapeutic responses and incidence of irAEs[40–42]. Correlative studies provide additional circumstantial evidence for such a mechanistic association, demonstrating the existence of shared T cell receptor sequences and/or upregulated organ-specific transcripts between tumours and non-malignant tissues affected by toxicities[43,44]. Furthermore, the occurrence of vitiligo (an

autoimmune response to melanocytes) provides a reliable indicator of antitumour activity of ICIs exclusively in patients with melanoma, also suggesting that irAEs and antitumour immunity might be mechanistically linked[45]. If these positive and negative outcomes do indeed arise from the same processes, long-term responders could have a higher risk of chronic toxicities than those who fail to benefit.

Evidence also exists suggesting that irAEs have mechanisms that are not related to antitumour activity, including those involving the microbiome, and viral or tissue-specific factors[46–51]. The divergence of irAEs is likely to be reflected in distinct and/or highly diverse mechanisms for each type of event. Notably, distinct cell types are implicated as dominant cellular populations and critical drivers in different preclinical models and biopsy samples obtained from affected tissues. For example, tissue-resident memory CD8+ T cells were the most abundant cell type in colon biopsy samples obtained from a cohort of patients with ICI-induced colitis, while cytotoxic activated memory CD4+ T cells were most prevalent in the brain of one patient with fatal encephalitis[49,50,52,53]. Targeted inhibition of particular cytokines, such as IL-6, could provide a method for uncoupling antitumour from antihost immune responses in preclinical models[54,55]. Ultimately, 'one size fits all' mechanistic explanations are unlikely to be forthcoming and might simply not exist: irAEs probably arise from both tumour-related and/or tumour-unrelated factors. Furthermore, the specific mechanisms of acute versus chronic irAEs remain poorly understood. A more detailed overview of the mechanisms of the various irAEs associated with ICIs is provided elsewhere[56].

Table 1 | **Long-term (>3-year) survival outcomes with ICIs in patients with metastatic disease**

Study	Design	Long-term survival outcomes	Unresolved irAEs (any grade)
Melanoma			
CheckMate-067 Phase III[22]	945 patients with unresectable stage III–IV melanoma received ipilimumab plus nivolumab (n = 314) vs nivolumab (n = 316) vs ipilimumab (n = 315)	5-year OS 52% vs 44% vs 26%	Skin toxicities in 16.6% vs 18.2% vs 11.9%; endocrine toxicities in 40.2% vs 17.5% vs 14.1%; toxicities affecting other organ systems seen in ≤3% of patients
KEYNOTE-001 Phase I[189]	647 patients (151 treatment-naive, 496 previously treated) with advanced-stage and/or metastatic melanoma received pembrolizumab	5-year OS 34% (overall) and 41% (treatment-naive patients)	NR
KEYNOTE-006 Phase III[190]	834 patients with unresectable stage III–IV melanoma received pembrolizumab (n = 556) vs ipilimumab (n = 278)	5-year OS 38.7% vs 31.0%	Skin toxicities in 16% vs 4%; endocrine toxicities in 16% vs 4%
NSCLC			
KEYNOTE-001 Phase I[191]	550 patients (101 treatment-naive, 449 previously treated) with locally advanced or metastatic NSCLC received pembrolizumab	5-year OS 23.2% (treatment-naive patients) and 15.5% (previously treated patients)	Endocrine toxicities in 12%; pneumonitis in 5%; skin toxicities and other toxicities including colitis and myasthenic syndrome all seen in <2% of patients
KEYNOTE-024 Phase III[192]	305 patients with previously untreated stage IV NSCLC with a PD-L1 TPS ≥50% received pembrolizumab (n = 154) vs chemotherapy (n = 151)	5-year OS 31.9% vs 16.3%	Colitis in 3.9% vs 0%; severe skin toxicities in 3.9% vs 0%; endocrine toxicities in 20.7% vs 3.3%; toxicities affecting other organ systems all seen in <2% of patients
RCC			
CheckMate-214 Phase III[193]	1,096 patients with previously untreated advanced-stage RCC with a clear-cell component received ipilimumab plus nivolumab (n = 550) vs sunitinib (n = 546)	4-year PFS 31.0% vs 17.3%	NR
Others			
CA209-003 Phase I	Patients with advanced-stage and/or metastatic melanoma (n = 107), RCC (n = 34) or NSCLC (n = 129) received nivolumab	5-year OS 34.2% (melanoma), 27.7% (RCC), 15.6% (NSCLC)	Skin toxicities in 28.1%; GI toxicities in 15.9%; endocrine toxicities in 10.7%; hepatic toxicities in 7.0%; pulmonary toxicities in 6.7%; toxicities of other organs seen in <3%

GI, gastrointestinal; ICI, immune-checkpoint inhibitor; irAEs, immune-related adverse events; NR, not reported; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TPS, tumour-positive score.

Timing and resolution

Distinct ICI regimens have disparate toxicity profiles. High-grade irAEs typically occur in a dose-dependent fashion with regimens containing anti-CTLA4 antibodies (30–55% for the combination of ipilimumab plus nivolumab), but are not dose-dependent with anti-PD-1–PD-L1 antibodies administered as monotherapies (10–15% incidence)[26]. The incidence, clinical presentation and management of the most common irAEs are discussed in more detail elsewhere[56,57]. To briefly summarize, these effects are more frequent in organs with extensive environmental interfaces (such as the skin, lungs, liver and gastrointestinal tract) or those harbouring presumed pre-existing, or smouldering, autoimmunity (such as the thyroid and joints). Nonetheless, irAEs can occur in essentially any organ system, including the heart, bone marrow, kidneys, bones, pituitary gland and others. IrAEs occur most often during the first three months of treatment but can arise at any time on therapy or even several months after treatment cessation[58]. Despite the lack of robust evidence from randomized clinical trials, acute severe irAEs are managed with reasonable effectiveness by providing symptom management, withholding ICIs and administering high-dose glucocorticoids (or potentially other immunosuppressive medications for steroid-refractory irAEs)[59–61]. In general, high-dose glucocorticoids do not appear to interfere with antitumour responses, although data from several studies suggest that administration of steroids within a few weeks of starting treatment might result in inferior outcomes[42,62,63].

The majority of irAEs arise early in the course of treatment, although delayed events, defined as irAEs arising after 1 year of therapy, are also possible. In one series of 118 patients, the estimated incidence of high-grade, delayed irAEs was 5.3%[64]. Many patients with delayed events had already reported an acute irAE (58%), although later events generally occurred at a distinct organ site (86%). The most frequent delayed irAEs were colitis, rash and pneumonitis, and two patients died from toxicities. Of note, most patients (74%) were receiving anti-PD-1 antibodies at irAE onset while 12% had discontinued within the previous 3 months and 14% had discontinued >3 months previously. These observations reinforce the idea that irAEs (either acute or delayed) can arise sporadically after discontinuation, but usually occur during active treatment. Thus, the possibility of developing delayed irAEs with extended durations of treatment should be considered when deciding whether to continue ICIs in patients with prolonged responses. Current data are limited, although possible approaches to guide this decision could include PET–CT or circulating tumour DNA (ctDNA)-based monitoring (with therapy cessation in patients with a metabolic complete response[29] and/or consistently undetectable ctDNA)[65–67].

The timing of irAE resolution is also not entirely understood. In theory, discrete immune perturbations, which include treatment with an ICI, resulting in autoimmune inflammation either could result in a temporary state that is reversible by withholding therapy followed by immune suppression and/or modulation if needed, or could incite an irreversible autoimmune disorder, particularly if the causative factor (ICI administration) is not withdrawn. The early clinical-trial experience largely suggests the former scenario, as most irAE symptoms improved or resolved upon treatment with high-dose glucocorticoids. Most syndromes and histopathological features seen in the involved organs closely mimicked autoimmune disorders, although genuine new-onset, chronic autoimmune diseases (such as lupus erythematosus or inflammatory bowel disease) have seemed extremely rare (with some exceptions, as discussed below). Despite this low incidence, chronic irAEs have emerged as a major clinical concern.

Chronic irAEs

Acute irAEs have thus far received the bulk of the attention owing to their more dramatic clinical presentation and need for urgent treatment. However, retrospective data published in May 2021 suggest that chronic irAEs (defined as those persisting for >12 weeks after discontinuation of an anti-PD-1–PD-L1 antibody) are more prevalent than previously recognized, occurring in 43.2% of patients[68]. This lack of recognition is likely to have occurred and persisted for several reasons. First, as noted, most acute irAEs will at least improve with steroids and often resolve altogether[69]. Second, adverse event reporting in clinical trials tends to focus on the most frequent treatment-related toxicities (those that occur in ≥10% of participants). Thus, low-frequency events are usually under-reported and under-recognized regardless of their aggregate prevalence. Third, most initial clinical trials have enrolled patients with metastatic cancer. Characterizing chronic and long-term events in patients with metastatic disease is challenging because these patients often have a limited life expectancy, thus constraining long-term follow-up. Such patients might also receive subsequent systemic therapies, surgery and/or radiotherapy, rendering toxicity attribution even more difficult. Finally, the presence of multiple co-morbidities, which is common in patients with cancer, might further impair the identification of chronic irAEs. Despite

Table 2 | Long-term outcomes of patients receiving ICIs as adjuvant or consolidative therapy

Study	Design	Long-term outcomes
Melanoma		
CheckMate-238 Phase III[194]	906 patients with resected high-risk stage III melanoma received nivolumab (n = 453) vs ipilimumab (n = 453)	4-year RFS 51.7% vs 41.2%; 4-year OS 77.9% vs 76.6%
KEYNOTE-054 Phase III[195]	1,019 patients with resected high-risk stage III melanoma received pembrolizumab (n = 514) vs placebo (n = 505)	3.5-year RFS 59.8% vs 41.4%; 3.5-year distant MFS 65.3% vs 49.4%
NSCLC		
PACIFIC Phase III[196]	713 patients receiving definitive concurrent chemotherapy or chemoradiotherapy received maintenance durvalumab (n = 476) vs placebo (n = 237)	5-year PFS 33.1% vs 19.0%; 5-year OS 42.9% vs 33.4%

ICI, immune-checkpoint inhibitor; MFS, metastasis-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.
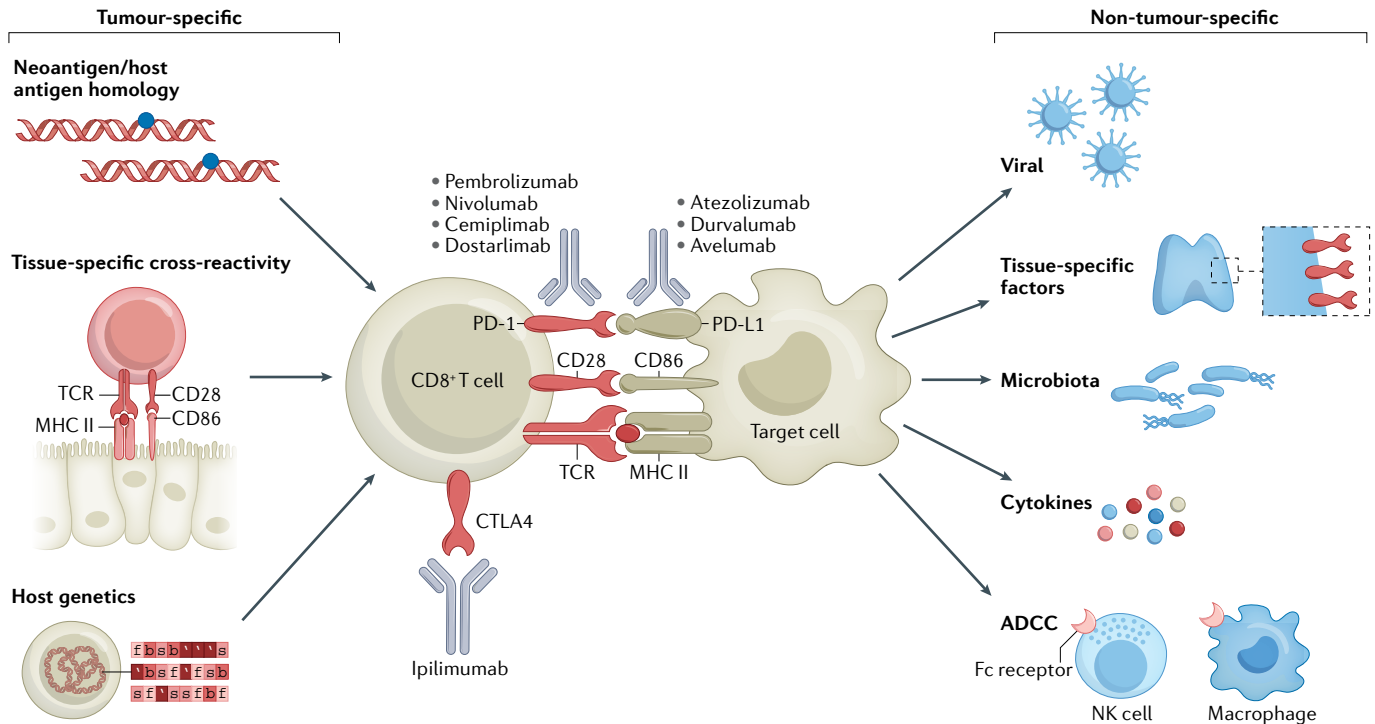
Fig. 1 | **Proposed mechanisms of immune-related adverse events.** Schema depicting the interaction of T cells with malignant or non-malignant cells, and the molecular mechanisms of immune-checkpoint blockade. Tumour-specific (left) and non-tumour-specific (right) aspects associated with the development of irAEs are also included. ADCC, antibody-dependent cellular cytotoxicity; NK cell, natural killer cell; TCR, T cell receptor.

these challenges, the durable clinical responses seen in a subset of patients receiving ICIs has enabled several follow-up studies to generate preliminary insights. In these studies, endocrinopathies (such as hypothyroidism and newly emergent type 1 diabetes) and rheumatological toxicities (such as arthritis) emerged as the most common chronic irAEs. Various other low-prevalence events also appeared, including neuropathy, dermatitis and pneumonitis[70,71], revealing a more nuanced picture of the possibility of chronic irAEs.

These observations raise the question as to why some irAEs fail to resolve. We hypothesize two distinct scenarios: burnout or smouldering inflammation. Burnout refers to irreversible damage of the relevant cells, thus precluding physiological recovery (FIG. 2). Endocrinopathies provide the archetypal example of this effect. In patients with ICI-induced forms of hypothyroidism (which is generally preceded by thyroiditis), hypophysitis or type 1 diabetes, the hormone-secreting cells are irretrievably damaged or ablated by the inflammatory process. Support for this notion includes the lack of recovery even with early utilization of high-dose steroids[72,73]. These syndromes are rarely reversible (in contrast to most other irAEs) and typically necessitate the use of exogenous hormone replacement therapy, suggesting that the relevant cell types are truly 'burned out'. Other irAEs might also fit into this category, including neuropathies (with persistently injured peripheral nerves) and xerostomia (with chronic salivary gland scarring leading to outflow obstruction and/or decreased saliva production). By contrast, a smouldering

inflammation phenotype might more closely resemble classic autoimmunity, in which ICIs trigger persistent subacute or chronic inflammation. ICI-associated inflammatory arthritis provides the classic example of this phenotype, in which the polyarticular involvement closely mimics that of rheumatoid arthritis (RA) in many patients and evolves into a chronic condition in approximately half of all affected patients[74]. The estimated risk of acute irAEs evolving into chronic events varies substantially between events (FIG. 3).

The definition of a 'chronic irAE' lacks a general consensus. In our retrospective study assessing patients with melanoma who received an adjuvant anti-PD-1 antibody, we defined these as irAEs lasting ≥12 weeks following treatment discontinuation[68]. By this definition, approximately 43% of patients had at least one chronic irAE. However, additional definitions could be proposed (including for those with longer-term manifestations), and multidisciplinary input will be needed to establish a consensus definition.

Endocrine irAEs. The earliest recognized chronic irAEs were those affecting the endocrine organs, as seen in 15–40% of patients receiving ICIs. Endocrine toxicities, unlike other irAEs, are usually not managed using high-dose steroids, as data from several small-cohort studies suggest that steroids have no effect on either initial severity or ultimate resolution[73,75]. Furthermore, these events do not necessitate ICI discontinuation; the cornerstone of their management is replacement of the relevant hormone[76].

Hypothyroidism is the most common endocrine irAE, occurring in around 10% of patients receiving anti-PD-1–PD-L1 antibodies as monotherapy and in up to 20% receiving ipilimumab plus nivolumab. Prior to hypothyroidism, approximately half of all patients have destructive thyroiditis resulting in excessive thyroid hormone secretions (thyrotoxicosis), which is often asymptomatic[77]. The median time to onset is approximately 6 weeks after commencing therapy, although hypothyroidism can arise at any time on

Pancreas

| Antibody | CD4⁺ T cell | CD8⁺ T cell | Cytokines | Macrophage | β-islet cell |

therapy[78]. The preceding thyrotoxicosis is generally transient, although the subsequent thyroid hormone deficiency tends to be a lifelong condition[75,79–81]. Systematic efforts to wean patients off thyroid replacement (to confirm persistence) have, to our knowledge, not been made, although anecdotally we have not been successful in our attempts to discontinue hormone replacement therapy in such circumstances. Of note, thyroid dysfunction seems to be associated with a superior prognosis, although as with other toxicity–survival associations, time-dependent variables might be confounding[82,83].

Hypophysitis is nearly unique to patients receiving ICIs. This condition occurs more often (5–10%) and with an earlier onset (median 9–12 weeks) in patients receiving ipilimumab-based regimens than in those receiving anti-PD-1–PD-L1 antibodies (<1%, median onset ~26 weeks)[72]. The predilection for those receiving ipilimumab seems to relate to expression of CTLA4 on the hormone-secreting cells of the pituitary gland, leading to antibody and complement binding[48]. Acutely, patients presenting with hypophysitis usually have symptoms of pituitary inflammation (headache, nausea and diplopia) and/or symptoms related to secondary adrenal insufficiency (fatigue and nausea). The inflammatory symptoms are generally transient, although hypopituitarism is usually permanent, and requires the replacement of glucocorticoids and often also thyroid and gonadal hormones[84]. Patients should receive the lowest physiological dose required to maintain quality of life (generally prednisone 5–7.5 mg daily or hydrocortisone 20–30 mg administered as two divided daily doses). Similar to hypothyroidism, hypopituitarism rarely resolves.

Other endocrine irAEs, although less common, are similarly persistent. ICI-induced diabetes mellitus (ICI–DM) occurs in <1% of treated patients but might present as diabetic ketoacidosis and generally requires lifelong insulin supplementation[85,86]. In marked contrast to hypophysitis, ICI–DM is almost exclusively seen in patients receiving anti-PD-1–PD-L1 antibodies, and only rarely with anti-CTLA4 monotherapy[87]. Serum amylase and lipase levels are often elevated at the time of ICI–DM diagnosis, suggesting that exocrine pancreatic inflammation might also have a role in pathogenesis, although whether persistent pancreatic insufficiency or chronic pancreatitis can frequently co-occur with ICI–DM is currently unclear[88]. Primary adrenal insufficiency is less common than hypopituitarism, albeit with a similar presentation, although this endocrinopathy might also
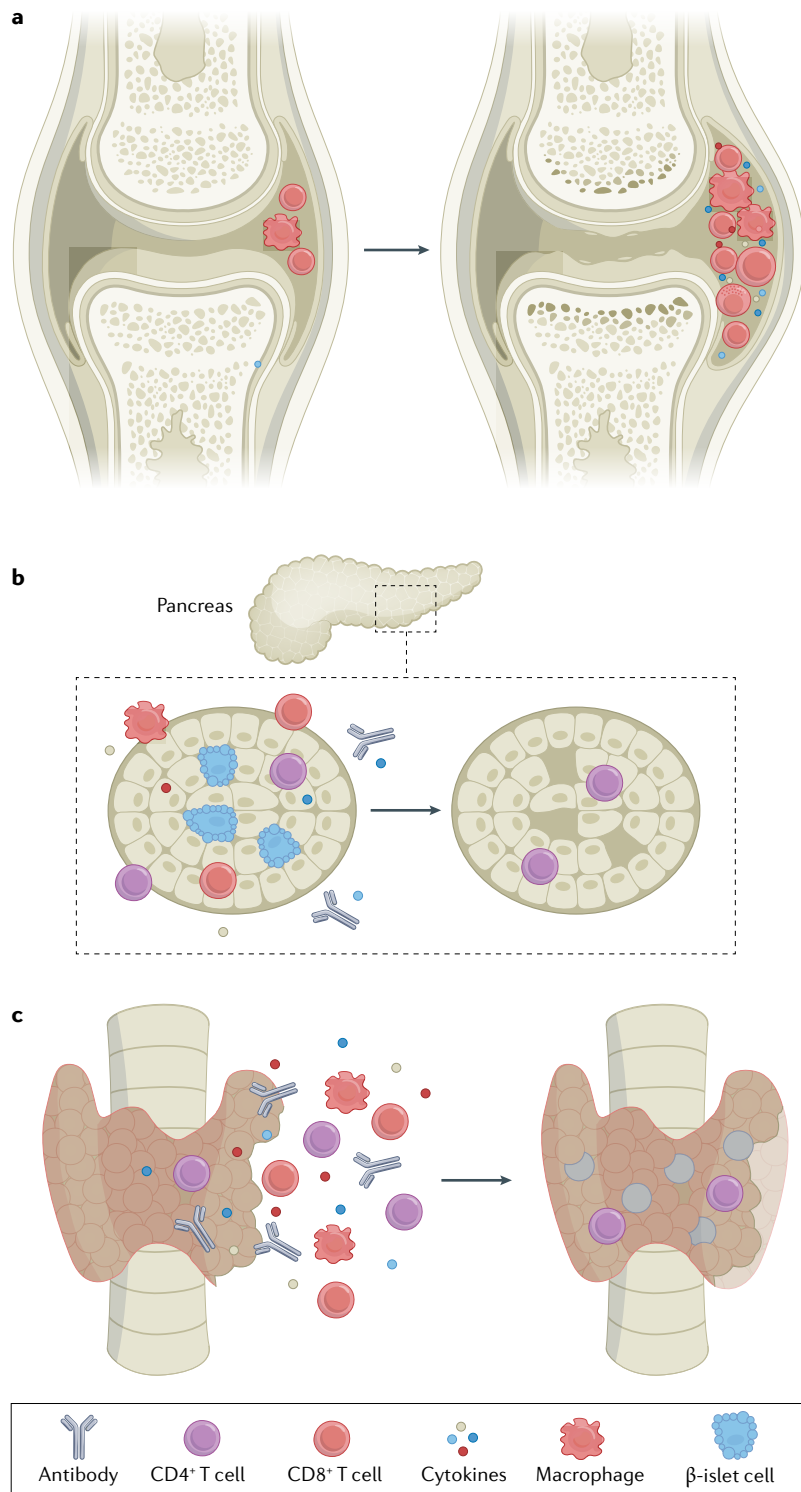
Fig. 2 | **Mechanisms of chronic immune-checkpoint inhibitor-mediated toxicity. a** | Smouldering toxicities characterized by off-target T cell activation that may wax and wane over time. Examples include rheumatoid arthritis-like inflammation of the joints. Such effects often resolve on treatment withdrawal and/or steroids **b**, **c** | Burnout toxicities characterized by irreversible damage to the relevant cells, typified by immune-checkpoint inhibitor-mediated endocrinopathies. Examples include destruction of the hormone-secreting cells of the pancreas (**b**) or thyroid (**c**). Such toxicities are usually irreversible and require permanent hormone-replacement therapy.

involve mineralocorticoid deficiency and thus present with hypotension[89].

The long-term effects of endocrine toxicities largely relate to the need to provide and maintain ongoing hormone replacement therapy rather than the presence of any chronic symptoms. Co-management with input from an endocrinologist might be helpful in optimizing the doses of replacement hormones and assessing for the uncommon cases where discontinuation might be possible. Assessment for hypogonadism is also warranted in patients with pituitary insufficiency. Studies involving fertility specifically in patients with hypopituitarism from ICIs, and studies on fertility in female patients treated with ICIs have, to our knowledge, not thus far been conducted. Data from several small cohorts suggest that male patients generally have preserved fertility following ICIs, although an inflammatory impairment of spermatogenesis remains possible in rare cases[90,91].

Rheumatological irAEs. Given the spectrum of rheumatological autoimmune disorders, the occurrence of a wide variety of rheumatological irAEs seems unsurprising. Interestingly, systemic lupus erythematosus and mixed connective tissue disorder are thus far not associated with ICIs, although syndromes resembling RA, polymyalgia rheumatica, polymyositis and Sjögren syndrome all occur, potentially providing clues to the pathobiology of these syndromes and the role of immune checkpoints[92]. These syndromes closely resemble established rheumatological conditions, although certain key differences also exist, including a lack of a genetic association with HLA-B*27, and certain key clinical distinctions. Specifically, inflammatory arthritis tends to arise in the large or medium joints with possible migration to small joints over time. While this syndrome most closely resembles RA, it also has features reminiscent of spondyloarthropathies, including enthesitis[93]. Most studies indicate that the majority of patients are seronegative (for rheumatoid factor or cyclic citrullinated peptide), although in one series all six patients were seropositive; thus, the true incidence is not clearly defined[93–95]. Approximately half of all patients have lingering symptoms of arthritis lasting at least 6–12 months after discontinuation of an ICI that, in our experience, will evolve into a truly chronic condition in a subset[96]. Furthermore, the response to steroids is often suboptimal in both the acute and chronic setting, as data from one series indicate that two thirds of patients require disease-modifying antirheumatic drugs (DMARDs)[97]. Notably, these data also suggest that the use of steroids and DMARDs is not associated with a worsening of oncological outcomes[97]. When patients develop a more chronic phenotype, non-steroidal anti-inflammatory drugs and other conservative measures suffice in certain patients, although chronic low-dose steroids or DMARDs are required in others. Data from small series suggest that ICI-induced chronic arthritis has major negative effects on quality of life, at least comparable to those of other irAEs[98]. Additional data are needed to quantify the long-term course in these patients. Among other rheumatological irAEs, ICI-induced sicca syndrome has similarities to and also differences from Sjögren syndrome, in that xerostomia predominates rather than eye involvement[99]. Most patients report subjective improvements with sialagogues and/or steroids, although salivary flow frequently remains suppressed[100].
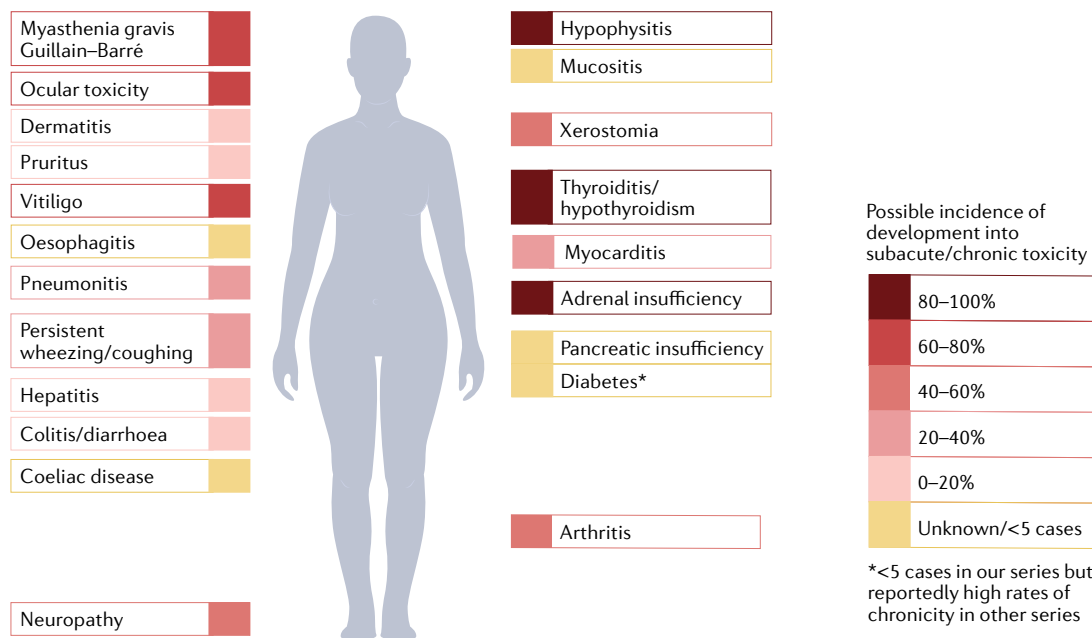

Fig. 3 | **Possible frequencies of chronic immune-checkpoint inhibitor-induced toxicities.** The exact risks of acute toxicities becoming chronic (defined as persisting for at least 12 weeks beyond treatment cessation) are currently unknown, although endocrinopathies, arthritis, xerostomia, neurotoxicities and ocular events are generally more likely to become chronic toxicities. Immune-related adverse events affecting the visceral organs seem to have a lower risk of becoming chronic. Percentages expressed are the percentages of acute toxicities that become chronic (defined as those that persist for at least 12 weeks following immune-checkpoint inhibitor discontinuation) from REF.[68].

A major challenging question, which is applicable to several organ systems but is most apparent in the context of rheumatological irAEs, is the management of chronic low-grade toxicities. Rheumatological irAEs might impair quality of life but are usually not sufficiently severe to justify ongoing high-dose steroids or ICI discontinuation (at least based on patient and/or physician preference). Thus, patients often continue to receive low-dose steroids and/or DMARDs in the presence of ongoing ICI therapy. The optimal strategy, in terms of optimal immunosuppressant choice or dose, timing of ICI discontinuation and antitumour outcomes remains poorly defined.

Gastrointestinal irAEs. Colitis occurs in up to 5% of patients receiving anti-PD-1 antibodies, and generally presents as diarrhoea and less often as abdominal pain and haematochezia. However, any grade diarrhoea (44%) or severe diarrhoea/colitis (15%) occur more often in patients receiving ipilimumab-containing regimens[27,101]. Hepatitis arises in 3–10% of patients (more often with ipilimumab-containing regimens) and is asymptomatic or might present as non-specific symptoms including malaise and myalgias, or less often as jaundice and acute liver failure. These high-profile events are major considerations in the acute setting but generally resolve with acute management and rarely evolve into a permanent phenotype (although symptoms can take multiple months to resolve, and thus meet the definition of chronic)[68,102,103]. Diarrhoea that fails to improve with steroids and/or other conventional immunomodulators (such as the anti-TNF antibody infliximab) should be evaluated carefully to rule out other causes, including ICI-induced coeliac disease, which has been reported rarely and necessitates a gluten-free diet (however, treatment-refractory colitis remains a more likely diagnosis than coeliac disease)[104]. Late-onset diarrhoea might also reflect pancreatic insufficiency. A 1% rate of steatorrhoea was reported in patients receiving anti-PD-1 antibodies in one cohort, with a median onset of 9 months[105]. Of note, 10% of this cohort developed radiographic signs of pancreatic atrophy, although the mechanisms and the clinical significance of this finding in asymptomatic patients remain to be seen. We are not aware of a chronic hepatitis phenotype that arises as a result of treatment with ICIs, although the possibility of subclinical liver injury, including following pre-existing liver inflammation (such as steatohepatitis), cannot entirely be ruled out.

Pulmonary irAEs. Pneumonitis is one of the major sources of both morbidity and mortality from anti-PD-1 antibodies, and most commonly presents as a dry cough, reduced oxygen saturation and bilateral ground-glass opacities (although a variety of distinct radiographic appearances can occur, including interstitial and organizing pneumonia). This presentation can overlap with that of COVID-19 or other viral infections, which should be ruled out[106]. Pneumonitis symptoms are usually responsive to steroids and/or second-line immunomodulation, although most patients have persistent imaging findings at least 1–2 years after symptom onset[107,108]. Most of these patients, however, have resolution of their symptoms, and detailed studies designed to assess for mild and/or subclinical decrements in lung function have not yet been performed. Paradoxically, data from preclinical models in at least one study suggest that anti-PD-1 antibodies could ameliorate ICI-induced pulmonary fibrosis[109]. We have also observed uncommon cases of patients with chronic wheezing or cough without radiographic evidence of pneumonitis with anti-PD-1 antibodies. Symptoms in these patients have generally improved over 6–12 months with inhalers and drug withdrawal, although we are not aware of any published reports in this area (and cannot completely rule out an atypical infectious trigger). Sarcoidosis might also complicate therapy but this is usually highly steroid-responsive (or will self-resolve) and rarely evolves into a chronic phenotype[110]. Reactivation of pulmonary tuberculosis can also occur[111,112], although data from a retrospective study suggest a similar incidence in patients with cancer who did not receive ICIs, thus making it unclear whether ICIs have a role in this effect[113].

Cardiovascular irAEs. Acute fulminant myocarditis was the first recognized cardiovascular irAE to be associated with an ICI, often presenting with electrocardiographic disturbances, including arrythmias and concurrent myositis[114,115]. However, increased recognition of this irAE and the resulting surveillance strategies led to the detection of more subtle forms of cardiac inflammation, ranging from smouldering myocarditis to asymptomatic elevations in serum troponin I[116–118]. An important unanswered question in the field relates to the long-term cardiac sequelae of these more subacute presentations of myocarditis. Extrapolating from non-ICI-associated myocarditis, one might expect that patients who recover from ICI-associated myocarditis would also have chronic consequences related to residual cardiomyopathy[119]. For example, skeletal muscle involvement can occur and might lead to paralysis or respiratory compromise (owing to diaphragmatic involvement) with the resultant complications of critical illness[92,120]. Other recognized cardiac sequelae include pericarditis, which is more common among patients with lung cancer receiving anti-PD-1–PD-L1 antibodies and is generally less fulminant and more responsive to corticosteroids[121,122]. Vascular irAEs have also been described and these include acute vasculitis, especially temporal arteritis and polymyalgia rheumatica[122]. In aggregate, these events are likely to occur in up to 1–2% of treated patients.

The more chronic sequelae of combination regimens involving an ICI and other traditional or targeted therapies is another important area of investigation, both of which might have their own inherent chronic cardiac toxicities[123]. An example is provided by the increasing use of ICIs in patients with breast cancer who previously received anthracyclines and radiotherapy[124]. Similarly, in patients with RCC and those with several other cancers, ICIs are often combined with VEGF inhibitors such as axitinib or lenvatinib, which have been associated with a number of cardiovascular sequelae including hypertension, vascular disease and cardiomyopathy[125].

Neurological irAEs. Neurological irAEs occur in up to 5% of patients and are more common with ipilimumab-containing regimens. These events can affect the neuromuscular junction (myasthenia gravis and Lambert–Eaton myasthenic syndrome), the central nervous system (meningoencephalitis) and peripheral nerves (both sensory and motor neuropathy, including Guillain–Barré syndrome)[126,127]. Meningoencephalitis usually resolves with acute management (although rarely can be fatal), and whether chronic deficits occur in some patients remains unclear. Myasthenia gravis might present with acetylcholinesterase receptor (AchR) positivity and evolve into a stereotypical chronic syndrome[128], but can also co-occur with myositis and myocarditis, and is often AchR-negative in this scenario. The long-term outcomes of ICI-associated myasthenia gravis are not well-characterized, although in most patients it appears to either completely resolve or remain controlled with disease-specific therapy[129,130]. ICI-associated Guillain–Barré syndrome has a high fatality rate (six of 31 patients (19%) in one series died of this irAE), and even patients whose symptoms do improve with immuno-modulation often have residual weakness and/or sensory loss (in one series, 68% of patients had residual symptoms)[126,131]. Peripheral neuropathy seems to be the neurological irAE that is most likely to evolve into a chronic phenotype[132]. Peripheral sensory neuropathy has been reported in approximately 2% of patients who received adjuvant anti-PD-1 antibodies for resected melanoma and nearly half of these patients developed chronic peripheral neuropathy[68].

Cutaneous irAEs. Skin toxicities are among the most common complications seen among patients receiving ICIs, and include various inflammatory dermatitis syndromes, pruritus and vitiligo. Dermatitis is usually manageable with topical or occasionally systemic steroids. Pruritus without rash might be the result of a neurogenic itch, and respond more effectively to GABAergic agonists (such as pregabalin) than to steroids[133]. These events often present a challenging clinical dilemma as bothersome but not life-threatening irAEs that do not seem sufficiently symptomatic to discontinue treatment or require high-dose steroids that nonetheless can negatively affect quality of life. Ongoing use of antihistamines, topical steroids and/or GABAergic agonists might all be required in patients with ICI-induced forms of dermatitis or pruritus. Involvement of a dermatologist in the co-management of cutaneous irAEs leads to higher treatment rates and even improved survival (potentially owing to the facilitation of ICI continuation)[134]. In our experience, even though dermatitis and pruritus frequently linger for weeks or months beyond treatment discontinuation, these irAEs tend to ultimately resolve (although this situation has not been well-defined in the literature, to our knowledge). Vitiligo, which is far more common in patients with melanoma than in those with other cancers, often fails to resolve and might become a lifelong complication. Severe cutaneous reactions, such as Stephens–Johnson syndrome and bullous pemphigoid, might also have life-threatening and/or long-term consequences[135].

Other irAEs. Similar to acute irAEs, a wide constellation of low-frequency events might ultimately become chronic. Nephritis, while usually steroid-responsive[136], required haemodialysis in approximately 10% of patients in one series; half of these patients failed to recover adequate renal function and required ongoing renal replacement therapy[137]. Haematological toxicities, including idiopathic thrombocytopenic purpura, aplastic anaemia, haemophagocytic lymphangiohistiocytosis and pure red cell aplasia can also all occur, albeit rarely, and might be fatal[138], although most of these irAEs resolve and do not evolve into a chronic condition[139]. Ocular symptoms might include uveitis and conjunctivitis, and can be managed using ophthalmic steroids[140]. We found that the few affected patients in our study often had chronic symptoms[68], although data from larger series of patients with ICI-related uveitis suggest that most patients have symptom improvement with treatment[141]. Other constitutional symptoms such as fatigue might also remain after ICI discontinuation, although, in our experience, this manifestation will usually ultimately improve and/or resolve. The pathophysiology, incidence and time course of these non-classic irAE sequelae have not been studied systematically.

Patients with pre-existing autoimmune disorders are largely excluded from clinical trials, and their long-term outcomes are not well described. Data from a number of studies suggest that these patients have similar or slightly higher rates of classic irAEs, and similar antitumour responses compared with those of individuals without autoimmune disease, although these patients also have high incidences of autoimmune flares (20–25%)[142–145]. In our anecdotal experience, any autoimmune disease flares will usually improve following treatment discontinuation, although the long-term outcomes in these patients need to be studied in more detail. Patients with a history of solid organ transplantation are another challenging population. These patients have a high risk of allograft rejection on receiving an ICI (approximately 50%)[146], which can lead to chronic complications (such as a need for long-term dialysis following rejection of a donor kidney) or have fatal consequences.

Fatal irAEs

Fatal irAEs are rare but can arise owing to overwhelming autoinflammation that is refractory to steroids and/or other immunosuppressants. Although these events clearly belong in a different category than chronic toxicities, the risks of fatal events need to be particularly considered in the context of the potentially durable responses generated by ICIs (such as early-onset fatal toxicity in a patient who might have had a response lasting years or even decades). These events highlight the need for effective rescue agents and rigorous studies to provide additional evidence-based approaches to the treatment of refractory irAEs[147–149]. Data from meta-analyses suggest that fatal irAEs occur at low rates, ranging from 0.4% with anti-PD-1–PD-L1 antibodies as monotherapy to approximately 1.2% with combination anti-CTLA4–anti-PD-1 regimens[150]. Although non-trivial, these fatality rates compare relatively favourably with those associated with cytotoxic chemotherapy, molecularly targeted therapy

and even high-risk surgical procedures for cancer[151–154]. The incidence of death from irAEs is also many-fold lower than that associated with cancer, even in indications with regimens that provide high durable response rates where toxicities are also a common occurrence. For example, in CheckMate-067, a phase III clinical trial in which patients with metastatic melanoma received ipilimumab 3 mg/kg and nivolumab 1 mg/kg versus either agent as monotherapy, two patients receiving this combination died of fatal toxicities compared with 130 cancer-related deaths at the last follow-up cut-off point[69].

Fatalities can arise from various organ-specific irAEs. Myocarditis is the irAE with the highest fatality rate (25–50% of patients)[114,115], largely owing to the refractory arrhythmias seen in severe cases. Myositis can also accompany myocarditis, resulting in diaphragmatic paralysis, respiratory failure and failure to gain independence from ventilatory support[92]. Pneumonitis is fatal in 10–15% of patients, generally owing to respiratory failure[155]. Hepatitis (from fulminant hepatic failure) and colitis (from colon perforation or less frequently from voluminous diarrhoea) can also cause death, although typically with a much lower incidence[102,103]. Neurological irAEs, while uncommon, can also be fatal in 10–15% of patients, often owing to refractory or prolonged Guillain–Barré syndrome, encephalitis or myasthenia gravis-like syndrome[126]. Of note, fatal irAEs often arise early in the course of therapy (earlier than most non-fatal events), at a median of 15 days (combination therapy) and 40 days (anti-PD-1 antibodies as monotherapy)[150], suggesting that pre-existing, organ-specific inflammation that is rapidly unleashed by ICI initiation might be responsible for these events. A trend towards older age of patients with fatal irAEs (compared with non-fatal events) has also been observed, suggesting that older age and the associated decreased functional reserve might predispose patients to a higher risk of death[150]. Prolonged immunosuppression might be the proximate cause of death in patients with protracted, refractory toxicities because the presence of opportunistic infections might also complicate the clinical course[156].

Clinicians should incorporate these non-negligible but low risks of fatal irAEs into treatment decision making in several ways. These risks of uncommon fatal irAEs are appropriately overshadowed by the near universal lethality of untreated metastatic cancer, particularly when considering potentially more toxic (and often less effective) alternative therapies. Nonetheless, for a subset of patients with low-risk disease, oncologists should consider the risks of fatal irAEs when selecting therapy. For example, patients with low-volume metastatic melanoma and/or severe co-morbidities could consider an anti-PD-1 antibody only, with combination therapy reserved for the onset of disease progression[157]. Analogously, in patients with very low-risk AJCC stage IIIA melanoma, withholding adjuvant therapy and treatment only on disease progression could be considered. Similarly, in patients with stage III *BRAF*[V600E]-mutant melanoma, BRAF/MEK inhibition might be considered in this setting[158], although the risks of cancer recurrence (and the often unclear risks of fatal toxicities with alternative treatments) must be taken into account.

These remain individualized decisions, however, and universal recommendations surrounding the risk of uncommon chronic or fatal irAEs remain challenging. Another point of contention surrounds monitoring and surveillance. Given the risk of fatal irAEs in patients receiving combination anti-PD-1 and anti-CTLA-4 antibodies (approximately 1.2%) and a typically early onset (median onset prior to the second dose), we recommend weekly laboratory and clinical monitoring for the first 3–4 weeks in patients receiving combination therapy, including testing for serum troponin I. One could reasonably argue that without clear data to support close monitoring, a 0.4% risk of fatal irAEs in patients receiving anti-PD-1 antibodies as monotherapy does not justify an analogous surveillance approach.

Implications for rechallenge

Another long-term implication of irAEs is whether patients who derived some benefit from treatment but also had severe toxicities should be rechallenged upon resolution of the irAE. In many patients this is an unnecessary consideration, particularly in those who have delayed irAEs after a complete response, or in those with clear disease progression on therapy. Nonetheless, clinicians might seek to rechallenge a subset of patients, including those with early-onset toxicities who might benefit from further therapy, or patients in whom an ICI was stopped while still responding and then later had disease progression.

Prospective data on the safety of rechallenge are currently lacking, although understanding certain key trends can assist in treatment decision-making. Data from retrospective studies suggest that recurrence of irAEs occurs in approximately 25–50% of patients rechallenged with anti-PD-1–PD-L1 antibodies[159–161]. De-escalation of therapy (such as de-escalation from combination anti-PD-1–anti-CTLA4 antibodies to anti-PD-1 monotherapy) seems to be associated with a lower risk of irAE recurrence (18% in one series), particularly for colitis (<5%)[162]. Determining which patients have the highest risk of recurrent irAEs is currently challenging; data from one series suggest that colitis, pneumonitis and hepatitis recur more frequently on rechallenge than do other irAEs; older age is also associated with irAE recurrence[159]. Data from other series suggest low rates of hepatitis recurrence, thus adding a further level of uncertainty[163]. A longer delay between discontinuation and rechallenge would also presumably decrease the risk of recurrent toxicities (for example, in a patient who is re-treated >12 months after discontinuing therapy owing to an irAE), although the data for such associations are currently not clear. Clinicians should consider both the type and severity of the irAE, as well as the clinical need for rechallenge in making decisions regarding the reintroduction of therapy. If rechallenge is undertaken, close clinical and/or laboratory monitoring should be used to assess for possible irAE recurrence.

A theoretical approach that has yet to undergo widespread clinical testing is to resume ICIs in conjunction with selective immunomodulatory therapy. Data from a series of five patients suggest that ongoing administration of infliximab enables the resumption of ICIs in
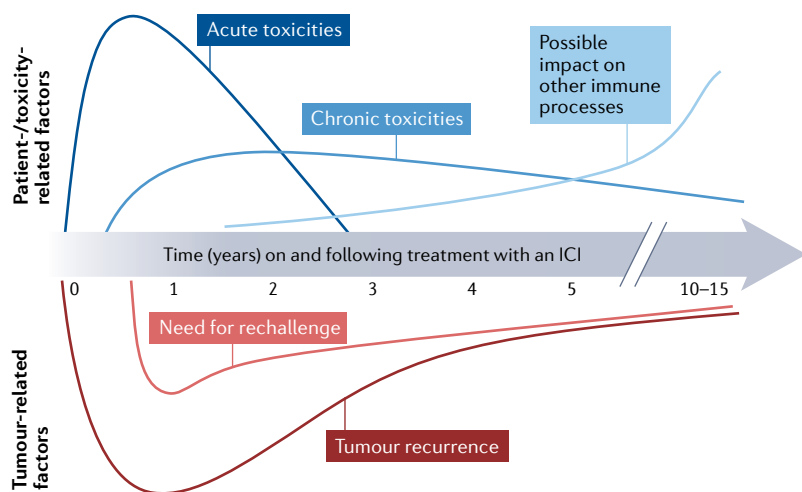
Fig. 4 | **Time course and potential importance of key issues throughout the course of treatment with immune-checkpoint inhibitors.** The relevant time frame of important patient-specific/toxicity-related factors (top), includes acute toxicities, which are largely relevant while patients are on therapy, chronic toxicities, which probably slowly decline over time, and the potential (theoretical) effects of such toxicities on other immune processes such as atherosclerosis, which could increase over time. Tumour-specific factors, including the risks of recurrence and the need for rechallenge, both of which appear to decrease over time are depicted below the timeline. ICI, immune-checkpoint inhibitor.

patients with colitis[164]. Data from preclinical studies suggest that this approach might even improve the anti-tumour activity of anti-PD-1 antibodies[165]. Similarly, targeted inhibition of cytokines such as IL-6 could theoretically uncouple antitumour immune responses from irAEs and permit safe rechallenge. Several studies testing these approaches clinically are currently ongoing (for example NCT03293784, NCT03999749 and NCT04940299).

Effects on other immune processes

Immune dysfunction has a role in many chronic diseases outside classic autoimmunity. Thus, perturbations involving prolonged treatment with ICIs could theoretically influence several diverse pathobiological processes including atherosclerosis, obesity and neuroinflammation, potentially over very prolonged timelines (FIG. 4). Data from preclinical models suggest that genetic inactivation of PD-1–PD-L1 potentiates the burden of atherosclerosis and promotes the infiltration of macrophages, CD4+ T cells and CD8+ T cells into atherosclerotic plaques[166,167]. Other high-dimensional sequencing studies of atherosclerotic plaques have shown high levels of CD8+ tissue-resident memory cells with both activation and exhaustion markers, identifying a cellular population with functions that could be activated or promoted using ICIs, potentially leading to atherosclerosis and/or plaque rupture[168]. Early clinical data support this concern: data from a matched cohort study indicate a threefold higher incidence of atherosclerotic cardiovascular events in the 2 years following ICI therapy compared with a similar pretreatment time frame[169]. However, conclusively linking this association epidemiologically can be difficult owing to the presence of several confounding variables, including ascertainment bias in patients with advanced-stage cancer, who are typically subject to more intensive clinical monitoring following diagnosis. Perhaps more convincingly, data from several small-cohort imaging studies suggest an increased incidence of progression of aortic plaques and inflammatory activity following treatment with ICIs[169,170]. The growing appreciation of inflammation as a major contributor to atherosclerosis provides evidence supporting the biological plausibility of this suggestion[171]. Intriguingly, data from a small-cohort study suggest superior oncological outcomes in patients receiving β-blockers, although several other studies suggest either no benefit or even potentially worse survival outcomes[172–174].

Regarding the effects of ICIs in patients with obesity, and the related obesity-mediated inflammation, preclinical studies suggest that adipose tissue T cells express markers of T cell exhaustion and that T cells have a key role in obesity-related complications (such as steatohepatitis). These observations raise the question as to whether ICIs might reactivate these T cells and exacerbate the severity of obesity and its related complications[175,176]. ICIs cause increased obesity-associated inflammation in the mammary fat pads of mice with obesity-associated breast cancer[177]. Interestingly, data from another model suggest that adipocyte-dependent *Pdl1* knockout results in decreased tumour growth but increased obesity-associated inflammation[178]. As an aside, several studies notably suggest that obesity correlates with improved responses to ICIs[179,180], although others have not found such an association[181,182]. Similarly, some but not all studies suggest that obesity might increase the risk of irAEs[181,183–185].

Data from a variety of studies demonstrate that post-injury inflammation (such as that seen following ischaemia and/or trauma) is associated with high levels of activated T cells and high levels of immune-checkpoint expression[186]. However, functional studies differ regarding whether PD-1–PD-L1 inhibition or gene knockout is either protective[187] or detrimental in this setting[188]. Similarly, inhibition of PD-1–PD-L1 has been reported to improve the pathology of both Alzheimer disease and tauopathy in mouse models, although this has yet to be clinically confirmed[189,190]. Clinical trials assessing the effects of modulation of immune-checkpoint signalling pathways on neurological processes might be an intriguing research direction in this challenging set of diseases.

Conclusions

The potential for durable responses, activity in a broad range of cancers and generally manageable toxicities has rendered ICIs an attractive and widely used treatment option for patients with cancer. This widespread use has broadened treatment-related and survivorship considerations beyond generating an antitumour immune response to lifelong effects on quality of life. In addition to chronic, classic irAEs, the long-term effects on global immune function triggered by blocking immune-checkpoint molecules remain unclear and need further study.

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