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Immune-related adverse events of checkpoint inhibitors

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Abstract

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Introduction (A.F-C); Epidemiology (A.P.); Mechanisms/pathophysiology (M.E.S-A); Diagnosis, screening and prevention (M.K.C, N.K, M.A.K, X.M.); Management (J.R.B, O.L); Outlook (M.R-C.); Overview of Primer (M R-C.).

Cancer immunotherapies have changed the landscape of cancer treatment during the past few decades. Among them, immune checkpoint inhibitors (ICIs), which target PD-1, PD-L1 and CTLA-4, are increasingly used for certain cancers; however, this increased use has resulted in an increased reports of immune-related adverse events (irAEs). These irAEs are unique and are different to those of traditional cancer therapies, and typically have a delayed onset and prolonged duration. IrAEs can involve any organ or system. These effects are frequently low-grade and are treatable and reversible; however, some adverse effects can be severe and lead to permanent disorders. Management is based primarily on corticosteroids and other immunomodulatory agents, which should be prescribed carefully to reduce the potential for short-term and long-term complications. Thoughtful management of irAEs is important in optimizing quality of life and long-term outcomes.

ToC blurb

Checkpoint inhibitors are increasingly being used in clinical practice; however, these therapies can be associated with adverse events that can affect almost any organ system. This Primer by Ramos-Casals and colleagues summarizes the epidemiology, mechanisms, diagnosis and treatment of these adverse events.

Introduction

Cancer immunotherapies are broadly defined as therapies that directly or indirectly target any component of the immune system that is involved in the anticancer immune response, including the stimulation, enhancement, suppression or desensitization of the immune system. These therapies comprise different approaches that include the use of specific drugs (monoclonal antibodies, small proteins or fusion proteins) that target proteins on the surface of cancer cells or immune cells, and other therapies, such as cytokines, oncolytic virus therapies, cancer vaccines or cell-based therapies (such as adoptive T cell transfer and chimeric antigen receptor T cell therapies).[1]

One class of these therapies — immune-checkpoint inhibitors (ICIs) — serve to induce an antitumour immune response by blocking immune checkpoints. Normally, immune checkpoints, key examples of which include CTLA-4 and PD-1 pathways, downregulate T cell responses and act to protect the body from possibly damaging immune responses, such as autoimmune disease (Fig. 1). However, tumours can hijack this system to evade the immune system, through the activation of immune checkpoints and inhibition of the T cell response. Thus, interfering with these immune checkpoint pathways can induce an antitumour immune response and convey therapeutic benefits in patients with cancer.

Several ICIs are approved for the treatment of various cancer types (Box 1). These drugs are all monoclonal antibodies that target either CTLA-4 signalling or PD-1 signalling (by targeting PD-1 or the PD-1 ligand, PD-L1), and have a universal effect on immune responses that is not dependent on individual cancer-specific antigens.[2] The use of ICIs for cancer therapy is increasing; however, a key challenge that has emerged with the progressive implementation of ICIs in clinical practice is their uncontrolled collateral effects on the immune system that can lead to so-called immune-related adverse events (irAEs).[3] ICIs have

a different spectrum of toxicities than standard chemotherapy or other biological agents, and most toxicities result from excessive immunity against normal organs [3] (Box 2).

Owing to the increased use of ICIs for cancer treatment, the cumulated annual number of irAEs is increasing exponentially, with nearly 13,000 cases reported up to 2018(Ref.[4]). More than two thirds of reported cases of cancer immunotherapy-related irAEs are related to ICIs, and only 3 drugs (that is, ipilimumab, nivolumab and pembrolizumab) are responsible for almost 60% of reported cases[4].

This Primer provides an update on ICI-associated irAEs (subsequently referred to as irAEs) from a multidisciplinary perspective. Owing to their increased prevalence and potentially severe nature, this Primer focuses on the adverse effects of ICIs only, rather than other types of cancer immunotherapy.

Epidemiology

Frequency of irAEs

Adverse events in clinical trials are reported and graded using the Common Terminology Criteria for Adverse Events (CTCAE) from the National Cancer Institute. CTCAE ranges from grade 1 to grade 5, which refers to mild, moderate, severe, life-threatening or death, in ascending order.[5] The general safety of ICIs has been estimated in a meta-analysis of 36 phase II/III trials, showing a pooled incidence ranging between 54% and 76% for all adverse events[6].

IrAEs can occur in any organ system, with the median onset usually within 2–16 weeks from the commencement of therapy, depending on the organ system involved[7]. However, onset of irAEs has been described within a few days of ICI initiation, and ≥1 year after completion of therapy.[8,9] The risk of first-onset irAEs is 3-fold higher during the first 4 weeks of treatment than between 4 weeks and the end of treatment.[10] As the T cell autoreactive clones that underlie these irAEs are presumably present long after the cessation of treatment, it is possible that irAEs may even present many years after treatment. Early toxicity (that is, between 1 and 12 weeks after treatment initiation) is most commonly dermatological effects for both CTLA-4 and PD-1 inhibitors.[11] Among individual ICIs, data from one meta-analysis showed that the most-common irAEs for ipilimumab are dermatological, gastrointestinal and renal toxicities, for pembrolizumab arthralgia, pneumonitis and hepatic toxicities, for nivolumab endocrine toxicities, and for atezolizumab hypothyroidism[6].

Pharmacological class-specific irAEs

Consistent with the distinct functions of immune checkpoints, the types of irAEs related to single drug therapy targeting the CTLA-4 or PD-1 pathways differ[12]. Typically, PD-1 and PD-L1 inhibitors are better tolerated than CTLA-4 inhibitors[13]; indeed, grade 3 and 4 irAEs were more common with CTLA-4 inhibitors than PD-1 inhibitors in one systematic review[14]. In this review, grade 3 or 4 irAEs comprised 31% of all irAEs for CTLA-4 inhibitors and 10% for PD-1 inhibitors); of note, colitis (OR 8.7, 95% CI 5.8–12.9), hypophysitis (OR 6.5, 95% CI 3.0–14.3) and rash (OR 2.0, 95% CI 1.8–2.3) were more common with CTLA-4 inhibitors, whereas pneumonitis (OR 6.4,

95% CI 3.2–12.7), hypothyroidism (OR 4.3, 95% CI 2.9–6.3), arthralgia (OR 3.5, 95% CI 2.6–4.8) and vitiligo (OR 3.5, 95% CI 2.3–5.3) were more common with PD-1 inhibitors[14]. The precise biological explanations for the differences in irAE localization and severity with different ICIs are not entirely known. Theoretically, CTLA-4 blockade might induce a greater magnitude of T-cell proliferation or reduced regulatory T cell (T_{reg})-mediated immunosuppression, and PD-1 blockade might activate a smaller number of T-cell clones[15,16] (although most circulating T-cells do not express PD-1, they can be induced to do so upon stimulation during TCR-dependent signalling)[15] (see Mechanisms/pathophysiology, below).

Few data are available about the potential differences in irAEs owing to the specific pharmaco-immunological composition of ICIs. However, some studies have demonstrated that antigenic effects of immunotherapies can result in the development of neutralizing antibodies and may depend on the degree of 'humanization' of the therapy[17]. Indeed, the formation of antibodies against biological agents is quite common, although these antibodies seem to have primarily neutralizing effects decreasing therapeutic efficacy and causing allergic or hypersensitivity reactions[18]. The immunogenicity of ICIs has been assessed in a few studies. In 6 clinical studies with nivolumab, anti-drug antibodies were found at least once in 12.7% of patients and persistently (detected in at least 2 consecutive samples, separated at least 16 weeks apart) in only 0.3% of patients without any clinical consequence (lack of association with hypersensitivity, infusion reactions, or loss of efficacy)[19], where as the maximum anti-drug antibody-positive rates were 54.1% for atezolizumab, 5.9% for durvalumab, 2.9% for avelumab and 2.1% for pembrolizumab[20]. Although the clinical implications of anti-ICI antibodies remain to be elucidated, these effects seem to primarily affect treatment efficacy rather than cause adverse events [20].

Combination strategies

Increasing use of combination strategies (combining immunotherapies with traditional treatments, such as chemotherapy, or the combining two types of immunotherapy) might improve the efficacy of cancer immunotherapy but could also amplify irAEs.[2]

With respect to the development of unexpected toxicities, combining chemotherapies with PD-1 inhibitors is not characterized by additional irAEs, and reported adverse effects are consistent with those of each agent.[21,22] Similarly, combining CTLA-4 inhibitors with PD-1 or PD-L1 inhibitors did not lead to unexpected new irAEs [15,16]. However, the frequency of adverse events with combinatorial therapy is higher than with monotherapy.[8] Indeed, in one study, the overall prevalence of irAEs (>90%) and severity (with grade ≥3 adverse events representing ~60% of the total irAEs) with combining CTLA-4 inhibitors with PD-1 or PD-L1 inhibitors were higher than that of monotherapy.[16]

In addition, the phenotype of the organ-specific irAEs can be modified with combination therapies. One study of 30 patients with clinically-confirmed arthritis demonstrated that individuals treated with combination ICI therapy were more likely to present with knee arthritis, to have higher levels of C-reactive protein, to have a prior irAE, and to have a reactive arthritis-like phenotype, compared with those treated with ICI monotherapy, who were more likely to have initial small joint involvement and arthritis as their only irAE[23].

Moreover, combination therapy was associated with greater risk and earlier onset of irAEs, with an up to 5-fold shorter median time to onset than monotherapy (32 for combination therapy versus 146 days for monotherapy).[10]

Tumour-specific patterns of irAEs

Overall, the types of irAEs do not seem to be specific to the type of cancer [12]. Indeed, although cross-study comparisons should be interpreted with caution, some data advise that the frequency of specific irAEs varies between individuals with different cancers who receive the same ICI, suggesting that different organ-specific immune microenvironments could drive specific irAE patterns in some types of cancer. For example, comparison of irAEs owing to PD-1 inhibitors in melanoma, non-small-cell lung cancer and renal cell carcinoma , showed that patients with melanoma had a higher frequency of dermatological (especially vitiligo) and gastrointestinal irAEs and a lower frequency of pneumonitis than patients with other cancers.[14]

Risk factors

The frequency of irAEs varies widely according to the ICI used and the organ-specific damage triggered, suggesting that there is a specific population of individuals who are prone to developing irAEs, maybe involving an unknown genetic background.[11] In addition, there are substantial individual variations in risks of irAEs, as some patients do not develop adverse events after months of therapy whereas others have life-threatening irAEs after a single infusion.

One explanation for the difference in risk of irAEs could be that some individuals have a predisposition to autoimmunity. To this end, some studies have reported that <10% of individuals who developed rheumatic irAEs had a family history of autoimmune disorders, and ~25% of individuals had a personal history of autoimmune disorders.[24–27] Furthermore, a number of *CTLA4* and *PDCD1* (encoding PD-1) polymorphisms have been associated with several autoimmune disorders.[28,29] Genetic variations could have a role in risk of irAEs, although no clear evidence of strong genetic associations have been demonstrated. Several studies have reported some personal risk factors linked to the development of irAEs. A history of autoimmune disease, use of CTLA-4 inhibitors and poor kidney function of grade ≥3 have been associated with a higher risk of developing irAEs.[30] In addition, one study has linked an elevated BMI with an increased risk of irAEs in patients treated with pembrolizumab[31], but this association was not confirmed in patients treated with atezolizumab[32] or ipilimumab[33]. By comparison, female sex and corticosteroid use were identified as protective markers against development of irAEs in one study of 78 patients treated with ipilimumab, nivolumab or pembrolizumab[30]. All these data require replication before firm conclusions regarding these associations can be drawn. Age has not been associated with a differentiated toxicity profile in patients treated with ICI monotherapy [34,35] and tolerance in elderly patients seems similar to younger people[34]. Whether other epidemiological features, such as patient’s ethnicity, are associated with risk of irAEs is unknown.

Mechanisms/Pathophysiology

CTLA-4 and PD-1 or PD-L1 inhibitors result in non-specific upregulation of immune pathways. Although there are commonalities between the immune toxicity profiles of these therapies, there are important differences in the frequency and clinical presentation of specific irAEs and the most frequently affected organs[14]. These phenotypic variations suggest that the mechanisms of irAEs differ between ICIs, although the precise mechanisms remain to be elucidated. Both CTLA-4 and PD-1 inhibition increases T cell activation and proliferation, abrogate T_{reg} functions, and possibly boosts humoral autoimmunity[36] (Fig. 2), although it is likely that specific pathways are more prominent in one therapy type versus the other, resulting in differences in irAE phenotypes.

T-cell activation

Studies in animal models that lack immune checkpoints or in patients with genetic disorders that affect immune checkpoints can be used to study the immunological consequence of immune checkpoint inhibition, and can shed some light on the mechanisms underlying irAEs. *CTLA4*-knockout mice develop profound and rapidly fatal T cell lymphoproliferation, hypergammaglobulinaemia and T cell-mediated autoimmunity.[37,38] Similarly, $CTLA4^{fl/fl}$ mice with acquired CTLA-4 deficiency during adulthood develop multi-organ autoimmune disease, although this disease is less severe than that observed in congenital deficiency.[37] In humans, two genetic diseases, CHAI (CTLA-4 haploinsufficiency with autoimmune infiltration) and LATAIE (LRBA deficiency with autoantibodies, regulatory T_{reg} cell defects, autoimmune infiltration, and enteropathy) which cause functional abnormalities in CTLA-4 pathways have been described, and result in widespread multi-organ lymphocytic infiltration, T_{reg} defects and autoantibody production[39]. Although the disease phenotypes in animal models and individuals with CTLA-4-related genetic disorders are substantially more severe than irAEs in patients who receive CTLA-4 inhibitors, they all have similar types of functional immune abnormalities.

Normally, T_{regs} express CTLA-4 and downregulate immune responses by inhibiting effector T cell proliferation and cytokine release, to maintain self-tolerance. In mice, administration of anti-CTLA-4 antibodies impairs T_{reg} function and survival via antibody-dependent cell-mediated cytotoxicity, therefore, increasing the ratio of effector T cells to T_{regs} in the tumour microenvironment[40], possibly enhancing antitumour responses and contributing to the therapeutic benefit observed with CTLA-4 inhibitors[40]. In accordance with these animal data , numbers of circulating T_{regs} are decreased in patients receiving ipilimumab with no significant changes in the relative frequencies of naïve, central memory and effector memory cells[41], although not all studies confirmed this reduction[42]. An imbalance in T_{regs} and T_h17 cells could contribute to irAEs associated with ICIs[43]. Enhanced T_h17 responses have prominent roles in the pathogenesis of many autoimmune diseases including rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease and many others[44] owing to the production of pro-inflammatory cytokines such as IL-17A, IL-21, and IL-22 by these cells. Indeed, CTLA-4 inhibitors increase numbers of circulating T_h17 cells in patients with melanoma, especially in those who developed irAEs [45], and increased IL-17 levels have

been associated with severe irAE, particularly colitis, in patients receiving ipilimumab, suggesting that the effect of ICIs on T_h17 cells contributes to the manifestations of irAEs [46].

PD-1 inhibition also enhances T cell activation, but results in different phenotypes of irAE than CTLA-4 inhibition. PD-1 is expressed on T cells, whereas its ligands PD-L1 and PD-L2 are present on antigen presenting cells, tumour cells and various normal tissues, and normally act to downregulate T cell activation (Fig. 1).[47] Both PD-1 and PD-L1 are expressed by T_{regs}, and this pathway appears to be involved in the differentiation of T_h1 cells into T_{regs}.[48,49] Mice deficient in PD-1 or PD-L1 develop various autoimmune manifestations depending on their genetic backgrounds, which, in some cases is mediated by autoantibodies, for example anti-troponin I antibodies in PD-1 deficient mice who develop cardiomyopathy.[50–52] PD-1 and PD-L1 inhibition with monoclonal antibodies leads to a decrease in the number of circulating T_{regs} that was associated with a more favourable progression-free survival in patients treated for melanoma [53].

In addition to these cellular changes, both CTLA-4 and PD-1/PD-L1 inhibition result in increased cytokine production. Indeed, blocking CTLA-4 with monoclonal antibodies in humans results in enhanced $CD4^+$ and $CD8^+$ T cell activation, with subsequent release of cytokines such as TNF, IFNγ and IL-2[15,54], which can lead to further T cell proliferation and activation. As discussed above, IL-17 might mediate irAEs given its marked pro-inflammatory functions, and the empirical evidence showing increased circulating levels in individuals with some irAEs, such as colitis[46]. The role of other pro-inflammatory cytokines is less evident, although there have been reports of increased IL-1Ra, CXCL10 and TNF levels in patients with irAEs.[55] Anti-TNF agents have been successfully used to treat different irAEs in patients receiving ICIs, suggesting a role for this cytokine in the development of these adverse events [56]. However, the precise roles of these cytokines in the development of irAEs is unknown and requires further study.

Cross-reactivity tumoural antigenicity

Cross-reactivity between antitumour T cells and similar antigens on healthy cells might underlie the development of some irAEs[57], such as vitiligo in patients with melanoma treated with ICIs.[58] Data from the ICIR-BIOGEAS Registry revealed that among 368 reported cases of vitiligo, 96% of cases were in patients with melanoma, which is suggestive of cross reactivity between T cells against tumour antigen and melanocytes.[11] In addition, cross-reactivity has been suggested for ICI-related myocarditis [59] owing to low selectivity among the tumour-reactive T-cell population, and, therefore, cross-reactivity with normal tissues.[8] In support of this mechanism, post-mortem tissue from two patients who received combination immunotherapy (CTLA-4 and PD-1 inhibitors) with fatal myocarditis had robust T-cell infiltration and clonal expansion with shared T-cell receptors in both myocardium and the tumour[60]. In one of the patients, a 10-fold increased expression of PD-L1 was demonstrated in affected cardiac tissue compared with non-diseased muscle tissue.[60]

B-cell mediated autoantibody production

Owing to increased T cell activation with ICIs, augmented T cell–B cell interactions can result in autoantibody production. Indeed, interactions between follicular T cells and B cells in germinal centres is vital for humoural immunity and abnormal interactions have been associated with autoimmunity[61]. The production of autoantibodies in mouse models of anti-CTLA-4-induced irAE is common.[62] Indeed, wild-type mice administered with repeated injections of anti-CTLA-4 antibodies develop anti-pituitary antibodies and hypophysitis (inflammation of the pituitary gland) is an irAE commonly observed with ipilimumab but not PD-1 and PD-L1 inhibitors.[62] Further data supporting a potential role for B cells in immunotoxicity is from recent data showing that patients treated with ICI had B cell changes after a single dose, including reduced numbers of circulating B cells and increased numbers of CD21lo B cells and plasmablasts. These early changes were strong predictors of subsequent irAE.[63]

The detection of autoantibodies during an adverse event would support an immune-mediated aetiology and could assist in guiding specific therapeutic intervention. To this end, several autoantibodies have been identified in some patients with specific irAEs, although their presence is not universal across patients. For example, autoantibodies to thyrotropin, FSH and corticotropin-secreting cells have been identified in patients with melanoma who received ipilimumab and developed hypophysitis[62]. Other examples of patients with irAEs and circulating autoantibodies against specific tissues after CTLA-4 or PD-1/PD-L1 inhibition[64] include anti-thyroid antibodies in patients developing thyroiditis, anti-BP180 antibodies in pemphigoid, and rheumatoid factor and anti-CCP in patients developing arthritis [62,65–69]. In addition, positive autoantibodies to diabetic autoantigens including GAD65, IA-2, ICA-512, ZnT8 and insulin have been found in some individuals with PD-1 inhibitor-associated type 1 diabetes mellitus

Despite the discovery of autoantibodies in patients who have developed autoimmune diseases after receiving ICIs, their frequency is significantly lower than that reported in patients with the same autoimmune disease who did not receive ICIs. This has been reported for type 1 diabetes mellitus[26], Sjögren syndrome[70,71], rheumatoid arthritis[72] or myasthenia gravis[73,74]. The predominant lack of serum autoantibodies may suggest a unique mechanism[23], although whether this finding reflects an underlying mechanism or the inability to detect as-yet unidentified autoantibodies or a very low level of the specific autoantibody involved is not well known.[8,23]

Direct effect of monoclonal antibody

As ICIs are monoclonal antibodies against molecules that are expressed by both immune cells and other tissues, it is likely that some irAEs could be caused by complement-mediated direct injury from these therapies. For instance, CTLA-4 is strongly expressed in the anterior pituitary[62], and hypophysitis is primarily seen with ipilimumab, not with PD-1 or PD-L1 inhibitors. In addition, myocardial PD-L1 is mainly localized on endothelium and is critical for control of immune-mediated cardiac injury[75], and a 10-fold increased expression of PD-L1 was demonstrated in the affected cardiac tissue in an individual with fatal myocarditis who received ICI combination therapy, compared with non-diseased muscle tissue.[60]

Diagnosis, screening and prevention

Organ-specific irAEs

We summarize the incidence, typical presentation and recommended clinical workup for the most frequent irAEs (a more detailed list is included in Box 1).

Cardiac.—Cardiac toxicity owing to ICIs is rare (occurring in <1% of patients[76] but can be fulminant and potentially fatal. Several cardiac pathologies have been reported associated with ICIs, of which myocarditis is one of the most common. Risk of myocarditis is higher with combination therapy than monotherapy.[60,77] The onset for myocarditis is a relatively early event, with most cases developing within ~4 weeks of a single dose of ICI.[77] Other cardiac irAEs include myocardial fibrosis, pericarditis, cardiomyopathy with Takotsubo-like syndrome, acute heart failure and cardiac arrythymia.[78,79] Clinical presentation of evolving cardiac irAEs can include dyspnoea (difficulty breathing), palpitations or symptoms of congestive heart failure (such as fluid retention and oedema), depending on the type of cardiac dysfunction, although preserved ventricular function assessed by echocardiography does not rule out possibility of cardiac arrhythmia.[77] Investigation of suspected cardiac toxicity should include electrocardiography and assessment of cardiac serum biomarkers including creatinine kinase and troponin levels. Useful imaging assessments include echocardiography to assess left ventricular ejection fraction and cardiac MRI with gadolinium enhancement to assess inflammation secondary to myocarditis.[5] Cardiac biopsy is the gold standard for diagnosing of myocarditis, and characteristic pathological findings consistent with immune cell infiltration of the myocardium support this diagnosis. The involvement of a cardiologist and close monitoring are necessary if myocarditis is suspected.

Dermatological.—A wide range of dermatological manifestations of varying severity can occur associated with ICIs including vitiligo, lichenoid dermatitis, psoriasis, bullous pemphigoid, granulomatous diseases, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and Sweet syndrome.[80–83] In most cases, dermatological toxicities occur early, and have been observed 2–3 weeks after ipilimumab treatment initiation and ~5 weeks after initiation of PD-1 inhibitors.[84,85] Although common with both CTLA-4 inhibitors and PD-1 inhibitors, pruritis, rash and vitiligo are usually low grade (mild and localized or widespread and intermittent) (Fig. 3).[86] Vitiligo-like depigmentation (VLD) is a characteristic cutaneous alteration predominantly described in patients with melanoma who receive ICIs, it has been reported in some untreated individuals and isolated cases in patients with non-cutaneous cancer.[87] Severe dermatological irAEs (that is, ≥grade 3 according to CTCAE) occur in only ~2–10% of patients receiving ICIs.[83,88] Expert input from dermatologists should be sought for progressive or high grade skin conditions, such Stevens-Johnson Syndrome, toxic epidermal necrolysis and DRESS syndrome [89]. Diagnostic work-up typically includes physical examination to assess the dermatological manifestations, and skin biopsies to histologically assess aetiology according to the dermatologist' clinical diagnosis.[90]

Endocrine.—The more commonly occurring endocrinopathies include hypophysitis, thyroid dysfunction and, less frequently, type 1 diabetes mellitus.[91] Endocrinopathies are

observed in up to 10% of patients who are treated with CTLA-4 inhibitors[92,93] and in 4–14% of those treated with anti-PD-1 inhibitors[94].

Hypophysitis has been reported in 3.3% of patients who receive ICIs in a meta-analysis of 61 clinical trials, with a higher rate in those who received CTLA-4 inhibitors (4.5%) and combination therapy (7.7%), whereas the rate in patients who received PD-1 or PD-L1 inhibitors was very low (in <1% of individuals)[95,96]. Symptoms of pituitary dysfunction can be nonspecific, including fatigue, headache or weakness with additional symptoms of headache or visual changes in those with hypophysitis causing pituitary enlargement.[97] Polyuria and polydipsia representing signs of diabetes insipidus and posterior pituitary hormone deficiency are more rarely reported than anterior pituitary hormone deficiencies[5,98]. Hypophysitis can lead to secondary adrenocorticotropic hormone (ACTH) deficiency with secondary adrenal insufficiency, hypogonadotropic hypogonadism and secondary hypothyroidism owing to thyroid-stimulating hormone (TSH) deficiency. Symptoms indicative of hypophysitis should prompt an evaluation of cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), TSH and free thyroxine (T4) levels, in addition to testosterone levels in men and oestrogen levels in premenopausal women. MRI of the pituitary gland should be carried out in patients presenting with neurological deficits to rule out tumoural involvement.[5] Although auto-antibodies against thyrotropin, FSH and corticotropin-secreting cells and expression of CTLA-4 on pituitary endocrine cells have been described in individuals with ICI-associated hypophysitis, testing for these markers is not part of routine workup.[62]

Thyroid dysfunction is one of the most common ICI-related endocrinopathies, and occurs slightly more frequently with PD-1 inhibitors than with CTLA-4 inhibitors.[99,100] Primary hypothyroidism of any grade occurs in 8–14% of patients treated with pembrolizumab,[96,101,102] whereas thyroiditis or hypothyroidism have been reported in 6% of patients with melanoma treated with ipilimumab and in 10–22% of patients treated with ipilimumab plus nivolumab.[92,96,103] ICI-associated thyroid dysfunction is typically mild (CTCAE grade 1–2) and mainly consists of hypothyroidism (which manifests with symptoms such as fatigue, increased sensitivity to cold, constipation or weight gain) and, less rarely, of hyperthyroidism (symptoms of which include weight loss, increased appetite, palpitations, irritability, tachycardia or arrhythmia). Hyperthyroidism can resolve to normal thyroid function over time although it can develop to hypothyroidism.[91,104] Investigation of thyroid dysfunction should distinguish between primary hypothyroidism (in which TSH level is high with low T4 levels) and secondary hypothyroidism (in which TSH and T4 levels are low and can be representative of pituitary dysfunction or hypophysitis).[99] Guidelines from the American Society of Clinical Oncology recommend monitoring thyroid function before ICI initiation and every 4–6 weeks during therapy, repeating testing annually or as indicated by symptoms[90].

Primary adrenal insufficiency is a less frequent irAE than secondary adrenal insufficiency related to hypophysitis with a reported frequency between 0.6 and 2.6%[94,95]. In severe cases, primary and secondary adrenal insufficiency can lead to adrenal crisis (a life threatening adrenal insufficiency caused by a lack of ACTH production in the pituitary gland in secondary adrenal insufficiency, or by lack of cortisol production in primary

adrenal insufficiency), symptoms of which include hypotension, electrolyte imbalances (particularly hyponatraemia (low serum sodium levels) and dehydration, and requires immediate treatment. Low cortisol levels can indicate primary or secondary adrenal insufficiency, which can be further differentiated with dynamic ACTH deficiency testing under specialist guidance. A lack of ACTH stimulation during dynamic ACTH testing indicates secondary adrenal insufficiency, although both primary and secondary deficiency likely require lifelong steroid replacement [94].

The ICI treatment emergent diagnosis of type 1 diabetes mellitus has been reported in ≤1% of patients treated with atezolizumab or pembrolizumab in phase III trials.[101,105,106] Type 1 diabetes mellitus associated with CTLA-4 inhibitors has not yet been reported with ipilimumab monotherapy.[91] Although rare, presentations with this irAE can be emergent, with 59% of individuals with ICI-associated type 1 diabetes mellitus presenting with ketoacidosis and 42% presenting with pancreatitis in a retrospective case series of patients receiving PD-1 or PD-L1 inhibitors.[26] Fasting glucose is the preferred diagnostic test for suspected new onset hyperglycaemia and testing for autoantibodies (against GAD65, IA-2, ICA-512, ZnT8 and insulin) may be considered as part of a more specific work-up, although patients are not always positive for these antibodies.[91]

Gastrointestinal.—Diarrhoea is one of the most common adverse events, and has an incidence of ~35% for CTLA-4 inhibitors, ~20% for PD-1 inhibitors and >40% for combinatorial therapy[107]. By contrast, colitis (evidence of inflammation of the colon) is reported in 12%, 1% and 14%, respectively[103]. Typical diagnostic workup for colitis can include assessments to exclude infectious causes and CT to evaluate the extent and severity of colitis and rule out bowel perforation (Fig. 3). Endoscopy is not routine for mild cases of colitis as correlation between the grade of diarrhoea and endoscopic features of colitis severity is poor[108] but can be helpful when diagnosis is elusive, in those with severe, refractory or recurrent colitis, to guide biopsy for the exclusion of cytomegalovirus-associated colitis or examine high-risk features that can guide escalation of therapy (ulceration or extensive colitis).[107,109] On colonoscopy, CTLA-4 inhibitor-related colitis can show mucosal erythema and ulcerations similar to those in Crohn's disease, although findings can be variable.[110] Colonic biopsies from individuals with ICI-associated colitis have shown both neutrophilic and lymphocytic inflammation, with a significant histological overlap with other etiologies of colitis making the differential diagnosis difficult[111]. Fatal intestinal perforation in individuals with severe colitis has been reported in up to 1% of patients who received ipilimumab, which was more commonly related to higher dose ipilimumab or ipilimumab combinatorial therapy with radiotherapy or other treatments.[112–114]

ICI-related hepatitis has a prevalence of 1–6% in anti-PD-1 or anti-PD-L1 trials, 1–25% in CTLA-4 inhibitor trials and 17–22% in combination anti-PD-1 and CTLA-4 inhibitor trials.[5,13,105,106,112,115–117] The most common presentation of hepatitis is an asymptomatic rise in transaminase levels, which is observed more frequently than increased bilirubin levels (which tends to only occur in very severe or chronic cases). Hepatitis screening via monitoring transaminase and bilirubin levels before initiating ICI and before every dose are necessary. Individuals who develop liver enzyme abnormalities should undergo additional

testing to rule out viral aetiology or disease-related hepatic dysfunction. In addition, a liver biopsy may be considered for those with higher grade hepatitis (defined as transaminases >5 times the upper limit of normal) to help expedite the identification of aetiology. For patients treated with ipilimumab, liver biopsies demonstrate changes overlapped with acute hepatitis similar to findings in drug-induced liver injury, acute viral hepatitis or autoimmune hepatitis.[118]

Haematological.—Haematological irAEs are rare (account for ~3–4% of the total irAEs) but can be potentially fatal.[119] The most common clinical presentations are neutropenia, autoimmune haemolytic anaemia, immune thrombocytopenia and aplastic anaemia.[119] Most haematological irAEs are asymptomatic and diagnosis is based on full blood count. However, severe cytopenias can present with fatigue and jaundice (haemolytic anaemia), purpura, bruising and/or bleeding from mucosal surfaces (thrombocytopenia), or fever and recurrent infections (neutropenia).

Neurological.—Neurological irAEs are rare but can cause substantial morbidity if not recognized and treated early.[120] When all neurological irAEs are pooled, an incidence of 3.8% for CTLA-4 inhibitors, 6% for PD-1 inhibitors and 12% with combination therapy has been reported in one review of 59 clinical trials.[121] Several neurological irAEs have been reported including peripheral neuropathies (reported in 1.3% of individuals with ICIs), myasthenia gravis (1.2%), myelitis (0.8%), meningitis (0.4%), encephalitis (0.3%) or Guillain-Barré syndrome (<0.1%).[121,122]

Several peripheral neuropathies have been associated with ICIs, including non-length-dependent polyradiculoneuropathies, small-fiber/autonomic neuropathy, mononeuritis multiplex, sensory neuronopathy and length-dependent sensorimotor axonal polyneuropathy123. Individuals with suspected neuropathies should undergo evaluation for alternative causes, as it could be caused by other medications, infectious disease and metabolic, endocrine or vascular disorders. Nerve conduction studies can be useful in this regard.[5]

Symptoms of myasthenia gravis include muscle weakness, commonly affecting the face. One review of 23 cases[73] of myasthenia gravis reported an average onset of symptoms within 6 weeks of initiating therapy and two-thirds of cases presenting with severe symptoms, with bulbar symptoms and myasthenic crisis (severe muscle weakness requiring respiratory ventilation) being observed more frequently in ICI-associated myasthenia gravis than in idiopathic cases[73].

Patients presenting with headache, neck stiffness and photophobia (extreme sensitivity to light) whilst using ICIs should raise suspicion for aseptic meningitis, which can be clinically distinguished from encephalitis owing to preserved mental status with aseptic meningitis (if mental status changes and seizures are present, encephalitis should be suspected). Investigations should include brain MRI with and without contrast in individuals with suspected meningitis or encephalitis, in addition to lumbar puncture to identify infectious causes (particularly viral aetiology) and electroencephalography to assess for subclinical seizures (Fig. 3).

Ocular.—Ocular irAEs encompasses inflammation of the eye, which can include uveitis, episcleritis, conjunctivitis and orbital myopathy, with an incidence of <1%.[124] Onset of uveitis associated with CTLA-4 inhibitors is usually CTCAE grades 1 or 2.[125] Symptoms of inflammation in the eye can include photophobia, pain in the orbital region, dryness and blurry vision.[126] A change in vision should prompt vision testing under the guidance of an ophthalmologist to assess visual acuity, pupil reactivity and fundus changes to diagnose uveitis[89].

Pulmonary.—Pneumonitis (focal or diffuse inflammation of the lung parenchyma) is a relatively rare irAE that is potentially life threatening[117,127]. Pneumonitis has an incidence of ~1 and 3% in individuals who received PD-1 or PD-L1 inhibitor monotherapy for melanoma, non-small-cell lung cancer and renal cell carcinoma[128], with the highest incidence of all-grade and high-grade pneumonitis in those with non-small-cell lung cancer (3.1%)[129]. One study reported a significantly higher frequency of all-grade interstitial lung disease (3.6% vs 1.3%) and high-grade interstitial lung disease (1.1% vs 0.4%) in patients treated with PD-1 inhibitors than those who received PD-L1 inhibitors[130]. However, some studies have reported a higher incidence, such as one study of durvalumab treatment after chemotherapy and radiotherapy in individuals with stage 3 non-small-cell lung cancer, in which incidence was 34%, supporting the hypothesis that radiotherapy could be a risk factor for pneumonitis.[131]

Patients with pneumonitis present most commonly with dyspnoea (shortness of breath) and cough but can also present with fever or chest pain[102], or as asymptomatic radiological findings in some individuals. The median time to onset of treatment-related pneumonitis for nivolumab was 15.1 weeks.[132] Suspicion of pneumonitis should be investigated by checking oxygen saturation on room air and while ambulatory, ruling out infectious aetiology, and CT to exclude alternative causes and evaluate the extent of inflammation. CT findings can be variable and include the following patterns: cryptogenic organizing pneumonia like, ground glass opacities, interstitial with interlobular septal thickening, hypersensitivity with a bronchiolitis like appearance and tree-in-bud (Fig. 3).[102] Bronchoscopy can also be helpful to establish diagnosis, particularly if alternative aetiologies are under consideration.[5]

Renal.—An overall incidence of 2.2% was reported for acute kidney injury (0.6% for grade III/IV renal events) in one systematic review of randomized controlled trials including 3,695 patients treated with ICIs[133], although more recent studies have suggested a higher frequency[134]. Increased serum creatinine levels are an almost universal feature of ICI-induced renal toxicity and most renal irAEs occurred 6-12 weeks following the start of ICI treatment[134]. An e valuation of potential alternative nephrotoxic therapies or contrast agents is suggested in individuals with newly-increased creatinine levels. In addition, investigation of urinary protein is recommended, followed by an autoimmune screen, including ANA, ANCA, rheumatoid factor, anti-dsDNA antibodies and serum complement levels, which might offer insight into the underlying pathological process.[5] Clinical findings and laboratory tests are suboptimal in diagnosing the underlying renal lesion, making kidney biopsy necessary in the majority of cases to definitely diagnose what type of renal damage is and potentially guide therapy[135]. Pathological features have been described as ranging

from acute tubulointerstitial nephritis to granulomatous features and evidence of thrombotic microangiopathy.

Systemic and rheumatic.—Systemic and rheumatic irAEs have mainly been reported in retrospective studies and case reports, and can be clustered into articular (with a prevalence of 36% in the ICIR-BIOGEAS Registry), muscular (prevalence of 34%), granulomatous (pre valence of 6%), vasculitic (prevalence of 12%) and systemic (prevalence of 12%) irAEs [136].

The most frequent articular irAEs are inflammatory arthralgias, arthritis (which manifest as joint inflammation and pain) and polymyalgia rheumatica (which manifests as stiffness and pain in the shoulders and hips). The frequency of arthralgias in randomized controlled trials of ICIs is 8% and are classified as mild (CTCAE grades 1 or 2 in >95% of cases, whereas arthritis has been reported in 1% of individuals[4] . The key features of articular irAEs include a median onset time of 70 days after ICI commencement, the predominance of seronegative arthritis (80% of individuals) and among individuals with available information about the distribution of the arthritis, ~60% were classified as polyarthritis[23,137–140]. Well-characterized inflammatory arthritis such as rheumatoid arthritis or psoriatic arthritis have been reported in ~30 individuals, with isolated reported cases of other forms (spondyloarthropathy, reactive arthritis-like, stenosing tenosynovitis, Jaccoud arthropathy, RS3PE syndrome, entesitis or osteonecrosis).[4] Patients receiving ICIs should be asked about joint symptoms, and referred as soon as possible to a rheumatologist if arthritis is suspected for diagnostic work up, which includes ultrasound/CT/MRI studies and analysis of serum inflammatory parameters and autoantibodies.

Muscular features can include myalgias and myositis, typical symptoms of which include varying degrees of muscle weakness and pain. The frequency of myalgias is 4% in randomized controlled trials, and they are often classified as mild (CTCAE grades 1 and 2), whereas myositis has been reported in 0.6% of individuals receiving ICIs.[4] Myositis is predominantly reported without a detailed clinical, immunological and histopathological characterization, with well-characterized inflammatory myopathies (dermatomyositis and polymyositis) being reported in ~20 cases, of which most cases were positive for myositis-related autoantibodies. Two specific studies[141,142] have characterized ICI-associated inflammatory myopathies, and have reported a mean time of onset of 25 days after ICI initiation and an association with other muscular irAEs (16–40% of people with inflammatory myopathies also had myocarditis or myasthenia gravis)and hepatitis (found in 8–10% of individuals with inflammatory myopathies). In addition, ICI-associated inflammatory myopathies are associated with a high mortality rate (21%), which was higher in patients who also developed myocarditis (52%).[141] Patients with a suspected muscular irAE should be investigated for raised serum muscular enzymes and myositis-related autoantibodies (Jo-1, PL-7/12, EJ, OJ, Mi-2, SRP, TIF, MDA5, PM-Scl, Ku, RNP and Ro) , and muscular involvement should be objectively assessed using electrodiagnostic and imaging studies and, whenever possible, with histopathology.

Granulomatous disorders, predominantly sarcoidosis (Fig. 3), are also an increasingly recognized irAE in patients treated with ICIs[143,4]. A review of 23 cases reported that sarcoidosis developed between 3 and 36 weeks after treatment initiation, with the

lymph nodes, lungs and skin bring the primary affected organs, although other systemic manifestations have also been reported.[144] A thoracic CT is mandatory in patients with suspected sarcoidosis. Histopathological confirmation of non-caseating granulomas in the absence of cancer progression and other causes (especially infectious) of granulomatosis is highly recommended for diagnosis.

Almost 200 cases of vasculitis associated with cancer immunotherapies have been reported, 64% of which are related to ICIs, mainly presenting with cutaneous purpura and less frequently as neuropathy or visceral vasculitis.[4] Based on the size of the vessel affected, giant cell arteritis is the most frequently reported systemic vasculitis (of which 28 cases have been reported[145]), with isolated reported cases of Schonlein-Henoch purpura, cryoglobulinemic vasculitis and eosinophilic granulomatosis with polyangiitis.[4,146] Patients with suspected vasculitis should be investigated for the presence anti-ANCA antibodies and cryoglobulins, and vascular involvement should be assessed using imaging and, whenever possible, with histopathological study.

Sicca syndrome has been reported in 5% of patients receiving ICI monotherapy and 10% receiving combination therapy in randomized controlled trials[4]. 22 cases of Sjögren syndrome triggered by ICIs have been reported, predominantly related to the use of PD-1 inhibitors[71,147]. Patients presenting with sicca symptoms after being treated with ICIs should be investigated for the presence of abnormal function of lachrymal and parotid glands, positive autoantibodies (mainly for anti-Ro antibodies) and focal lymphocytic sialadenitis via histopathological analysis of minor salivary glands. In addition, isolated cases of systemic sclerosis, lupus and antiphospholipid syndrome have been reported in individuals receiving ICIs.[24,138,148,149]

Screening and prevention

Safety and efficacy in patients with pre-existing autoimmune diseases.—As ICIs can induce irAEs, and given that patients with pre-existing autoimmune diseases were excluded from clinical trials of ICIs, the safety and efficacy of these drugs in this population is a key issue before extending treatment recommendations to include these patients.

Several studies have suggested an enhanced risk of irAEs in patients with pre-existing autoimmune diseases. A systematic review that included 123 patients with pre-existing autoimmune disease and treated for cancer by ICIs[150] demonstrated autoimmune disease exacerbation in 50% of individuals, de novo irAEs in 34% and no autoimmune symptoms in only 16%. Interestingly, no difference was observed in patients with active versus those with inactive pre-existing autoimmune disease, and patients receiving treatment for their autoimmune disease at initiation of cancer immunotherapy had a little fewer adverse events (59%) than those who did not receive treatment at initiation of immunotherapy (83%). Further evidence supporting an increased risk of irAEs in those with autoimmune disease is based on data from the systematic REISAMIC registry[151], the prevalence of irAEs was higher in patients with pre-existing autoimmune diseases (44%) compared with patients without autoimmune diseases (29%), of which 55% of irAEs in patients with previous autoimmune disease were related to the same autoimmune disease and 45% were new-onset irAEs. In this study, ICIs were stopped only in five of 20 patients with irAE and the

overall survival of the patients with previous autoimmune diseases was the same as in the patients without. In many patients, irAEs were manageable with corticosteroids (only 16% required other immunosuppressive therapies) and discontinuation of ICIs was required in 17% of patients in the systematic literature review[150] and in 11% of individuals in the Gustave Roussy experience[151]. Thus, even if the risk of irAEs is higher in patients with pre-existing autoimmune disorders, there is no reason to exclude these patients from cancer immunotherapy [152].

The rates of reactivation or flare of the pre-existing autoimmune diseases after initiating ICIs are summarized in Fig. 4 (Supplementary Figure 1 and Supplementary Table 1)[150,151,153–159].

Autoimmune screening before starting therapy.—One of the most common factors that predisposes to autoimmune diseases is the presence of autoantibodies without clinical signs[160]. Some patients with irAEs might have pre-existing subclinical autoimmune conditions that manifest clinically as a full autoimmune disease after ICI therapy. There is no argument for recommending a universal screening for auto-antibodies before initiating ICI as even if an individual screens-positive, it will not be a contraindication for treating them with ICIs for cancer therapy. However, in patients with a personal or familial history of autoimmune diseases, or in those who presented signs or symptoms suggesting an underlying autoimmune disease, screening for autoantibodies may be considered before starting ICI, since these patients have an enhanced risk of developing a full autoimmune disease after treatment and therefore, should be followed up more closely.

Potential markers predicting occurrence of irAEs.—Some biomarkers that are present before starting ICI therapy are associated with a high risk of occurrence of irAEs. Several studies have linked the presence of pre-therapeutic serum autoantibodies with an increased risk of some irAEs[8], such as myositis in patients with anti-mAChR antibodies[161], thyroiditis in patients with anti-thyroid antibodies[162], dermatological irAEs in those with anti-BP180 antibodies[163], colitis in patients with antinuclear antibodies[164], hypophysitis in those with anti-GNAL antibodies or anti-ITM2B antibodies and pneumonitis in those with anti-CD74 antibodies[165]. B cell changes detected after a median of 3 weeks of starting ICI therapy (reduced number of total B cells, increased percentage of CD21low B cells and plasmablasts and greater clonality in CD21low B cells) has also been suggested to help identify patients at increased risk of irAEs.[63] Serum cytokine levels might also provide predictive value and mechanistic insight for patient susceptibility to ICI-induced irAEs; for example, pre-existing, circulating IL-17 levels may help to predict which patients with ipilimumab-treated melanoma could develop severe diarrhoea and colitis, since patients who developed grade 3 CTCAE colitis had higher mean IL-17 serum levels than those who presented with grades 0-2[166] All these data have to be confirmed in larger studies before recommending its use in clinical practice.

Management

Therapeutic management

Treatment of irAEs depends on the organ system affected and the grade of toxicity according to the CTCAE classification, although it should be emphasized that common CTCAE grading might not be useful to grade the severity of some complex irAEs (such as systemic and rheumatic irAEs). Therapeutic algorithms have been developed by several organizations to help simplify and effectively diagnose and manage these adverse effects (such as ASCO, NCCN, ESMO, SITC and EULAR).[88–90,152,167] To summarize, patients with CTCAE grade 1 irAEs typically do not require interventional treatment, and in most cases ICIs can be continued or temporarily halted with close monitoring. Patients with grade 2 adverse effects should stop ICIs until adverse effects abate, although glucocorticoids can be considered in some individuals, depending on the severity of the organ-specific damage or if irAEs persist after ICI therapy is stopped, where patients presenting with grade 3 or 4 irAEs should initially receive steroids In general, grade 1 irAEs can be treated and monitored by the patient's oncologist (particular for non-bullous dermatitis, colitis, hepatitis, ocular, renal, musculoskeletal and haematological irAEs), whereas patients with grade >2 irAEs or those with symptomatic endocrine irAEs such as diabetes mellitus or thyroid disease should be referred to a specialist. For some organ-specific irAEs (pancreatitis, hypophysitis, pneumonitis, neurological, rheumatic and systemic autoimmune diseases), referral to a specialist should be strongly considered regardless the degree of CTCAE severity.

Here, we follow a pharmacologically-guided schedule about the overall therapeutic approach for irAEs; for more detailed organ-by-organ management guidelines, the reader is directed to guidelines. [88–90,152,167]

Glucocorticoids.—Glucocorticoids are the mainstay of treatment for irAEs except for endocrine irAEs (Fig. 5). Prednisone is usually the preferred corticosteroid and the dose varies depending on the grade and clinical severity[88–90,167] and for most irAEs, is tapered slowly over 4–6 weeks if clinical improvement is confirmed within days of steroid initiation. In those with grade 3 or 4 irAEs, methylprednisolone pulses can be started, and if clinical improvement is confirmed after 48–72 hours, then tapered slowly over 4–6 weeks. As a general rule, glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease, and in case of anticipating a prolonged use, the need for introducing steroid-sparing strategies or an early initiation of anti-TNF and other monoclonal antibodies. Although endocrine irAEs are common they rarely require treatment with steroids , steroids can provide symptom relief in patients presenting with pituitary or thyroid gland acute inflammation.[168] The prophylactic use of glucocorticoids is not recommended for the prevention of irAEs as some study showed that did not prevent the development of diarrhoea or colitis in patients receiving ipilimumab monotherapy[169].

Hormonal replacement.—Typically, patients with symptomatic thyroid dysfunction, hypopituitarism, hypoadrenalism, or type I diabetes mellitus are given replacement hormones or insulin. These irAEs rarely recover fully, so patient's often require permanent treatment[94,170] especially for the corticotrope axis dysfunction. In addition, holding ICI

is not required for endocrinopathies unless the patient is symptomatic or unstable. ICI treatment can resume once replacement therapy or treatment is started for the endocrine irAE.[89]

Non-steroidal immunosuppressive agents.—If irAEs do not markedly improve within 48–72 hours of steroid treatment, or cannot be tapered without a flare of the symptoms, synthetic immunosuppressive agents should be added as glucocorticoid-sparing agents, with no evidence supporting the choice of one drug over another. For example, mycophenolate-containing immunosuppressants can be used for management of steroid-refractory irAEs particularly for immune-related hepatitis, nephritis, pancreatitis and uveitis, while patients with steroid-refractory pneumonitis can be treated with either mycophenolate or cyclophosphamide,[89] and those with arthritis can receive hydroxychloroquine or methotrexate[171]. Other immunosuppressive therapies have been less frequently used for corticosteroid-refractory irAEs including tacrolimus, cyclosporine and sulfasalazine.[89] Use of these drugs should be considered only for refractory irAEs in addition consultation with appropriate disease specific specialists.

Intravenous immunoglobulin and plasma exchange.—Intravenous immunoglobulin (IVIG) is used as a second-line therapy for neurological and haematological irAEs.[172] IrAEs that are caused directly by autoantibodies, such as some haematological or neuromuscular irAEs can also be treated by plasma exchange (Fig. 5)[173], which can remove the pathogenetic autoantibody from the circulation and is particularly effective in severe cases of myasthenia gravis or Guillain-Barré syndrome.

Monoclonal antibodies.—Non-controlled descriptive studies have suggested the use of infliximab (a TNF inhibitor[174]) for severe, refractory immune-related colitis or inflammatory arthritis. In most cases, only a single dose of infliximab is required to improve these irAEs; however, a second dose 2 weeks later is required in some patients. One study has demonstrated that the frontline addition of infliximab to glucocorticoids for grade 3 and 4 colitis was associated with a significantly shorter time to symptom resolution, compared with patients who received glucocorticoids alone.[175] In a mouse model of colon cancer, anti-TNF monoclonal antibodies prevented the occurrence of colitis concomitantly administered with combined CTLA-4 and PD-1 inhibitors and increased survival, providing clinically feasible strategies to dissociate efficacy and toxicity in human trials[176]. Prior to administering TNF inhibitors, tests to identify infectious disease, such as a tuberculosis spot test, should be performed as TNF inhibitors can increase the risk of reactivation of certain infections.[89,174]

Vedolizumab (a monoclonal antibody against the integrin α4β7 that inhibits the migration of T cells into inflamed gastrointestinal mucosa can be used instead of infliximab for immune-related colitis.[177] The theoretical advantage of using vedolizumab is that the immunosuppression would be limited to the gastrointestinal tract and, therefore, spares the systemic immune suppression. In a retrospective study of patients refractory to steroids (n=19) and infliximab (n=9) who received vedolizumab, 86% achieved a sustained clinical remission and 54% an endoscopic remission[178].

Tocilizumab (an anti-IL-6 antibody) has been suggested for the management of some steroid-refractory irAEs.[179] One study in people with nivolumab-associated grade 3–4 irAEs (n=34; predominantly pneumonitis, serum sickness and systemic inflammatory response syndrome or cerebritis) reported a clinical improvement in 80% of patients who received tocilizumab , which, in most cases, required only 1–2 doses to cause clinical improvement.[180] Another study has reported the effective use of tocilizumab in three cases of severe polyarthritis.[56]

Other monoclonal antibodies have also shown some promise for the treatment of some steroid-refractory irAEs. Rituximab has shown efficacy for treatment of glucocorticoid-refractory cases of severe encephalitis,[181] autoimmune cytopenias[182] or severe bullous skin disease.[183] In addition, two cases of successful response to abatacept[184] or alemtuzumab[185] have been reported in patients with steroid-refractory autoimmune myocarditis.

Despite the benefits of monoclonal antibodies for treatment of steroid-refractor irAEs, they are associated with specific adverse effects that may preclude their use for some irAEs (Fig. 5). For example, anti-TNF antibodies should be used with caution to treat pneumonitis because can risk exacerbating interstitial lung disease [186], as well as etanercept and tocilizumab to treat colitis due to their association with increased risk of inflammatory bowel disease [187] and increased risk of perforation in patients with Crohn's disease [188,189], respectively. Moreover, some cases of progressive multifocal leukoencephalopathy during therapy with natalizumab (anti-α4-integrin monoclonal antibody) — although not with vedolizumab [190] — have been reported and the use of anti-integrin monoclonal antibodies for neurological irAEs should be proposed with caution.

Follow-up and monitoring

The therapies used for the management of irAEs can be associated with adverse effects, of which, some can be severe. Whether treatment of irAEs affects the treatment of the cancer (Box 3) and when to reintroduce ICIs to the patient are important questions.

Adverse effects and infections.—Most irAEs resolve after a median of 4–8 weeks after the ICI is stopped, or with the addition of glucocorticoids in severe cases.[115,191] Close monitoring is mandatory to detect a relapse of the irAE or a complication of immunosuppressive therapies. Some adverse effects can be easily identified, such as worsening of pre-existent diabetes mellitus, hypertension and mood disorders, whereas others, such as infections, are more challenging to detect. Although ICIs do not seem to directly increase risk of infection,[190] the use of immunosuppressive therapies and biological agents to treat irAEs may increase the risk[192] . A retrospective study in 740 patients with melanoma who received CTLA-4 and/or PD-1 inhibitors identified severe infections (defined as infection requiring hospitalization or parenteral antimicrobials) in 54 (7%) patients (steroids were used in 46% and infliximab in 16% of these patients). In this study, opportunistic infections were reported but most infections were bacterial pneumonia or septicaemia, and the main factors significantly associated with severe infection were the use of corticosteroids or infliximab[192]. Owing to the overlap with intestinal, pulmonary and hepatic irAEs, some opportunistic infections should be always ruled out in patients

in whom irAEs did not improve or worsen despite treatment with immunosuppressive agents. Infections to be ruled out include cytomegalovirus[193] and Clostridium difficile[194] in refractory colitis, *pneumocystis* pneumonia, pulmonary aspergillosis[195] and tuberculosis[196] in pneumonitis, and viral infections or reactivations (hepatitis B virus and cytomegalovirus) in hepatitis[197–199]. Thus, a history of previous infections and risk factors for viral infections such as HIV or viral hepatitis should be evaluated before individuals with cancer are given ICIs [196,200] although a chronic viral hepatitis infection with negative viremia are not contraindication for an ICI prescription as shown in liver carcinoma studies with PD-1 inhibitors[201].

Rechallenge.—In the ASCO and ESMO guidelines, permanent discontinuation of the ICI is recommended for all grade 4 irAEs, and the ASCO guidelines recommend permanently stopping ICIs for those with grade 3 myocarditis, pneumonitis, nephritis, hepatitis and severe neurological toxicities. In the remaining cases, the oncologist has to determine if a patient will benefit from the reintroduction of ICI therapy (rechallenge) once the irAE has resolved. No randomized phase III trials evaluating ICIs rechallenge after resolution of grade ≥2 irAEs have been published, and the main evidence available comes from studies with more than ten patients rechallenged [202–205]. These studies showed that 33–50% of the patients who had an irAE during treatment with a PD-1 or PD-L1 inhibitors had a recurrent or new-onset irAE after reintroducing PD-1 or PD-L1 inhibitors, in contrast to 18–21% of those who had an irAE during combination treatment (with CTLA-4 and PD-1 inhibitors) after reintroducing only PD-1 inhibitors. Three deaths were reported in patients rechallenged due to Steven-Johnson syndrome, colitis and hepatic failure, and pneumonitis. In all these studies, patients with myocarditis or severe neurological irAEs were not rechallenged, therefore, data from these conditions are lacking.

The decision to rechallenge should be based on the potential risk/benefit ratio for each patient. When to re-initiate ICIs should be undertaken by a multidisciplinary committee involving organ specialists in each cancer centre to provide recommendations with a personalized care/patient centred approach. No risk factors associated with irAE relapse after rechallenge have been clearly identified, except a shorter time to the initial irAE, and the increased risk of relapse after resumption of CTLA-4 inhibitors than for PD-1 or PD-L1 inhibitors[205].

Quality of life

Health-related QOL

Studies have addressed health-related quality of life (HRQOL) issues faced by people with irAEs, which have been shown to have a greater effect on older patients and potentially influence quality of life.[206] Several studies have demonstrated that ICIs are well tolerated compared with other anticancer therapies[207–209], and that even grade 3 and 4 irAEs does not translate into clinically meaningful differences in HRQOL[210]. By contrast, other studies have demonstrated significantly lower HRQOL scores than the general population[211,212], increased psychological morbidity[213], or a potential effect on cognitive function of survivors patients who received these therapies[214]. More people with melanoma and brain metastasis

are surviving for longer owing to ICIs, and efforts to further comprehensively address psychosocial, neurocognitive, and HRQOL issues in this population are ongoing[212].

Outcomes

Patients who developed irAEs often show a better therapeutic response to cancer compared with those who do not develop irAEs, suggesting a close link between autoimmunity and the antitumour effect elicited by ICIs[215, 100]. Indeed, a growing body of evidence suggests that patients who have irAEs have marked improvements in progression-free survival, overall survival and overall response rate than those who did not develop an irAE, with more consistent data in patients treated with PD-1 and PD-L1 inhibitors[215] than in those treated with CTLA-4 inhibitors[3]. Of the different organ-specific irAEs that are associated with enhanced survival, the most consistent data are from dermatological irAEs, particularly rash and vitiligo[216,217]. However, many questions remain about what irAE-specific factors (such as affected organ, severity, timing of onset or therapeutic intervention) could have a prominent role in contributing to the increased survival [215].

Despite these apparent benefits in terms of cancer outcomes, the development of irAEs has been related to an irreversible organ damage and in some cases can be fatal. Irreversible organ damage is most frequently reported for irAEs of the endocrine system, which predominantly result in permanent damage or destruction of the endocrine organs and often require chronic therapy[60]. In addition, PD-1 inhibitors have been associated with a higher incidence of grade 3 or 4 pneumonitis (leading to irreversible fibrotic pulmonary damage)[218], and severe colitis might require colectomy in some patients who have perforation[219]. Moreover, isolated cases of non-resolved xerostomia, alopecia or vitiligo with ICIs have been reported[220].

The global rate of irAE-associated fatality is estimated as ~0.6% of treated with ICIs patients, with individual rates of 0.36% for patients who received PD-1 inhibitors, 0.38% for those who received PD-L1 inhibitors, 1.08% for those who received CTLA-4 inhibitors and 1.23% for individuals who received combined therapy.[221,222] The reason for fatality differed widely between regimens; for example, 70% of CTLA-4-related deaths were due to colitis , whereas fatalities associated with PD-1 and PD-L1 inhibitors were often from pneumonitis (35%), hepatitis (22%) and neurotoxicity (15%).[221] Among patients who received combination therapy (with PD-1 and CTLA-4 inhibitors) and died, 37% of deaths were caused by colitis and 25% by myocarditis.[221] In addition, the time to fatal effects varied depending on the ICI used; fatalities occurred early after ICI initiation for combination therapy, with a median time from symptom onset to death of 14.5 in comparison with 32 days for monotherapy[221]. Myocarditis has the highest demonstrated mortality rate, reported in 48% of 351 individuals included in the two main studies[223,224]. The mortality rate of myositis is reported in 20% of 204 individuals,[138,141,225,226] in whom the principal cause of death was associated myocarditis.[141,226] A similar mortality rate has been reported for ICI-associated myasthenia gravis in 26% of individuals (n=35),[73,74] whereas the rate is lower for colitis (6%).[224] Other irAE-related deaths have been reported for interstitial lung disease,[227–229] hepatitis,[228] Guillain-Barré syndrome[114] or autoimmune cytopenias.[230]

Outlook

International efforts are needed to develop evidence-based multidisciplinary management guidelines for irAEs, improve clinical characterization and diagnosis of irAEs, and anticipate that the certain rapid incorporation of novel therapeutic approaches could increase the diversity and severity of irAEs. The main aim of future research should be the development of more-effective therapeutic managements, which will require further clinical trials, and efforts to develop more precise mechanistic studies to learn more about pathophysiology.

Implications for treatment

The risk of irAEs with ICIs has several implications for cancer treatment, namely, whether the use of these therapies is appropriate and efficacious in individuals with chronic disorders. Data is now emerging from early phase II trials and case reports that suggest durable responses and a manageable safety profile of ICIs in patients with controlled hepatitis B or hepatitis C virus infection.[231] With respect to the use of ICIs in patients with HIV, no unexpected irAEs have been observed.[232] By contrast, data from case series suggest that there is a high risk of graft rejection with PD-1 and PD-L1 inhibitors in patients with solid organ transplantation and although responses to ICIs have been observed, the use of these therapies in this population should be weighed against the risk.[233] Tolerance of ICIs in those ≥65 years seems similar to in younger individuals,[34] although older patients should be closely monitored for cardiovascular disease.[234] Compliance with vaccine recommendations is also important for protecting patients with cancer who are immunocompromised,[235] and one study has demonstrated that influenza vaccination in patients with lung cancer receiving PD-1 inhibitors does not induce irAEs.[236] With this complex clinical scenario, a multidisciplinary approach is mandatory[237], with a central role for an oncologist,[238] rheumatologist[239] and internist,[240] together with the support of the specialist of the affected organ/s.

Improving clinical characterization

The wide heterogeneity of both pharmacological and clinical scenarios of irAEs, together with the increasing identification of these events, suggest that the use of artificial intelligence (machine learning) and big data (incorporating large volumes of information into computers) will have a key role in optimizing clinical characterization.[241,242] A key limitation for optimal clinical characterization of irAEs in randomized controlled trials is the use of CTCAE[88] as these criteria can be difficult to apply and do not allow accurate reporting of the severity and effect of some irAEs, such as rheumatological or systemic irAEs.[88] In addition, many randomized controlled trials only report adverse events of grade ≥3 and exclude those with lower severity[27]. One study has underscored critical challenges in assessing the occurrence, type, timing, and severity of irAEs, showing a poor inter-observer agreement for most organ-specific irAEs (except hypothyroidism).[243]

Some data from large databases such as the Vigibase[145] or the ICIR-BIOGEAS Registry[4] have begun to show a potential organ-driven clusterization of irAEs. Although >95% of irAEs are reported as single-organ autoimmune diseases, there is likely a publication bias,

especially in cases reported in randomized controlled trials and pharmacovigilance studies in which irAEs are always counted as single-organ effects. However, a specific cluster of phenotypic associations among muscular irAEs (for myositis, myocarditis and myasthenia gravis) has been reported, particularly for the coexistence of myositis and myocarditis (which overlap in one third of reported cases),[225] whereas rheumatic and systemic irAEs may be clustered into 5 differentiated clinical phenotypes.[4] Future potential applications of artificial intelligence in cancer care and research must develop worldwide cancer networks and registries that investigate differential presentations and outcomes of irAEs according to individual, environmental or drug-related factors.[241]

Understanding environmental modulation

One rapidly expanding field is the effect that microbiota composition has on the efficacy and toxicity of ICIs.[179] Understanding the effect of the microbiome on the immune response will be essentialin enabling the treatment of dysbiosis and to re-establish equilibrium of the protective gut microflora to limit and treat irAEs. The first irAEs in which a key effect of microbiota composition has been reported is for colitis, whereby patients with high levels of Bacteroidetes phylum have a decreased risk of colitis[11], together with the use of adjunctive 'oncomicrobiotics' that have been proposed to indirectly promote beneficial immune responses through optimizing the gut microbiome.[244] The first case series of successful treatment of ICI-associated colitis with fecal microbiota transplantation has been reported, with reconstitution of the gut microbiome and a relative increase in the proportion of T_{regs} within the colonic mucosa, lending further support to the hypothesis that alterations in the microbiota are involved in ICI-colitis.[245] More than 200 fecal microbiota transplantation clinical trials are being carried out worldwide, but the knowledge of this microbial therapy is still limited, especially with respect to how the viabilities of transplanted microbiotas should be assessed.[246] Determining the influence of non-gastrointestinal microbiota and whether irAEs are influenced by microbial composition and other environmental or geographical factors are critical.[166]

Future cancer immunotherapies

Newer-generation cancer immunotherapies and combination therapies will likely be associated with an enhanced prevalence of irAEs. [2] Combinatorial therapies pembrolizumab and avelumab with the multi-tyrosine kinase inhibitor axitinib has been approved in late 2019 for the treatment of advanced renal-cell carcinoma , with hypothyroidism (25-35%) and arthralgias (18-20%) being the most frequent reported irAEs[247,248]. In addition, the janus kinase inhibitor tofacitinib may enhance delivery of antibody-based therapeutics to tumour cells through modulation of inflammatory cells in a mouse model[249] and could serve as a rationale for conducting trials in which short-term tofacitinib is administered with ICIs. In addition, other forms of immunotherapy, such as B cell targeting therapies, therapies targeting innate immunity including natural killer (NK) cell-targeting therapies are gaining interest.[2] New bispecific antibodies, alternate antibody-based structures (which target multiple tumour and immune components simultaneously and could selectively enhance localized, tumour-targeted immune activity), and dual immunomodulators (targeting inhibitory PD-1 and LAG-3 or targeting stimulatory OX40 and inhibitory CTLA-4) are also in the horizon. As chimeric antigen receptor T-cell therapies become more widely

used for cancer treatment, it is likely that these therapies will be tested in future trials in combination with ICIs. Chimeric antigen receptor-T-cell therapies have been shown to induce toxicities such as the cytokine-release syndrome (characterized by high fever, hypotension, and multiorgan toxicity) and CAR-T-cell-related encephalopathy syndrome (CRES, characterized by symptoms of confusion and delirium, seizures and cerebral oedema .[250]

As different routes of immunotherapy administration can influence their toxicity profile, with increasing interest in intratumoural therapies, it will be important to know whether more localized immunotherapies affect the frequency and severity of triggered irAEs. To minimize off-tissue effects, delivery systems have been designed for local and sustained release *in vivo* and many systems, including nanoparticles, scaffolds, hydrogels and cells, can be loaded with multiple therapeutic agents that are chosen on the basis of targets identified in patient biopsy samples, although whether these systems reduce the development of irAEs requires further study.[251]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

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Box 1.

Approved ICIs according to cancer type.

Anti-CTLA-4 antibodies

- Ipilimumab
  - Colorectal cancer[a]
  - Melanoma
  - Renal cell carcinoma [a]

Anti-PD-1 antibodies

- Nivolumab
  - Bladder cancer
  - Colorectal cancer
  - Head and neck cancer
  - Hepatocellular carcinoma
  - Hodgkin lymphoma
  - Melanoma
  - Non-small cell lung cancer
  - Renal cell carcinoma
- Pembrolizumab
  - Bladder cancer
  - Cervical cancer
  - Gastroesophageal junction cancers
  - Head and neck cancer
  - Hepatocellular carcinoma
  - Hodgkin lymphoma
  - Merkel cell carcinoma
  - Metastatic solid tumours classified as MSI-H or dMMR
  - Non-small cell lung cancer
  - Primary mediastinal large B-cell lymphoma
  - Stomach cancer
- Cemiplimab
  - Cutaneous squamous cell carcinoma

Anti-PD-L1 antibodies

- Atezolizumab
  - Bladder cancer
  - Breast cancer
  - Non-small cell lung cancer
- Avelumab
  - Bladder cancer
  - Merkel cell carcinoma
- Durvalumab
  - Bladder cancer
  - Non-small cell lung cancer

[a]In combination with nivolumab. ICIs, immune checkpoint inhibitors.

Box 2.

Organ-based classification of irAEs in patients with cancer treated with ICIs.

Cardiac

- Myocarditis[a]
  - Autoimmune myocarditis
  - Myocardial fibrosis
- Pericarditis
  - Autoimmune pericarditis
  - Pericardial effusion
  - Pericardial tamponade

Dermatological

- Alopecia areata/universalis
- Dermatitis herpetiforme
- Erythema multiforme
- Granuloma annulare
- Lichen planopilaris/planus/lichenoid dermatitis
- Panniculitis/Erythema nodosum
- Pemphigoid/Pemphigus
- Psoriasis
- Pyoderma gangrenosum
- Sweet syndrome
- Vitiligo[a]

Endocrine

- Adrenitis[a]
  - Adrenal insufficiency
  - Cortisol deficiency
  - Hypercortisolism
  - Hypoadrenalism
  - Isolated ACTH deficiency
- Autoimmune diabetes mellitus
- Hyperparathyroidism

- Hypogonadism
- Hypophysitis[a]
  - Autoimmune hypophysitis
  - Hypopituitarism
  - Panhypopituitarism
- Thyroiditis[a]
  - Autoimmune thyroiditis
  - Hyperthyroidism
  - Hypothyroidism
  - Graves disease
  - Thyrotoxicosis

Gastrointestinal

- Enterocolitis[a]
  - Ileitis
  - Ileocolitis
  - Ischemic colitis
  - Microscopic colitis
  - Ulcerative colitis
- Hepatitis[a]
  - Autoimmune hepatitis
  - Eosinophilic hepatitis
- Lymphocytic gastritis
- Pancreatitis

Haematological

- Aplastic anemia/pure red cell aplasia
- Autoimmune hemolytic anemia
- Autoimmune neutropenia
- Hemophagocytic lymphohistiocytosis
- Immune thrombocytopenic purpura

Muscular

- Myalgias[a]
- Myositis[a]

  - Antisynthetase syndrome
  - Bulbar myopathy
  - Dermatomyositis
  - Diaphragmatic lymphocytic polymyositis Polymyositis
  - Necrotizing myopathy
  - Orbital myositis

Neurological

- Aseptic meningitis
- Encephalitis
- Cranial nerve involvement
  - Bilateral hearing loss
  - Facial palsy
  - Oculomotor paresis
- Motor neuropathy
  - Acute generalized motor neuropathy
  - Multifocal motor block neuropathy
- Myasthenia gravis
- Neuromyelitis optica spectrum disorders
  - Optic neuritis
  - Transverse myelitis
- Polyneuropathies[a]
  - Axonal sensory motor polyneuropathy
  - Multiplex mononeuritis
  - Peripheral sensory neuropathy
- Polyradiculopathies
  - Chronic inflammatory demyelinating polyneuropathy
  - Guillain-Barré syndrome

Ocular

- Conjunctivitis
- Episcleritis/scleritis
- Orbital inflammation
- Uveitis[a]

  - Anterior uveitis
  - Chrorioretinopathy
  - Iridocyclitis/iritis
  - Panuveitis
  - Posterior uveitis
- Vogt-Koyanagi-Harada syndrome

Pulmonary

- Interstitial lung disease[a]
  - Alveolitis
  - Organizative pneumonitis
  - Pneumonitis
  - Pulmonary fibrosis
  - Pulmonary hemorrhage

Renal

- Acute tubulointerstitial nephritis/renal tubular acidosis
- Glomerulonephritis

Skeletal

- Arthralgia [a]/polyarthralgia
- Arthritis[a]
  - Monoarthritis
  - Oligoarthritis
  - Polyarthritis
- Entesitis
- Fascitis/Eosinophilic fascitis
- Jaccoud arthropathy
- Polymyalgia rheumatica
- Psoriatic arthritis
- Rheumatoid arthritis
- Spondyloarthropathy
- Tenosynovitis

Systemic

Antiphospholipid syndrome

- Lupus
  - Lupus nephropathy
  - Subacute cutaneous lupus erythematosus
  - Systemic lupus erythematosus
- Sarcoidosis
  - Cutaneous sarcoidosis
  - Pulmonary sarcoidosis
  - Renal sarcoidosis
- Sicca syndrome[a]/Sjogren syndrome
- Systemic sclerosis
- Vasculitis[a]
  - Cerebral vasculitis
  - Cryoglobulinemia
  - Cutaneous vasculitis
  - Eosinophilic granulomatosis with polyangiitis
  - Giant cell arteritis
  - Pulmonary vasculitis
  - Schonlein-Henoch purpura

[a]More than 100 cases reported[4]. ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events.

Box 3.

Treatment of irAEs without affecting cancer treatment.

Whether the use of steroids and/or immunosuppressants to treat immune related adverse events (irAEs) could reduce efficacy of cancer immunotherapy has been evaluated in several studies. In this regard, results from retrospective studies in melanoma were reassuring; steroid use was not associated with a loss of efficacy of CTLA-4 inhibitors and PD-1 or PD-L1 inhibitors[256,257]; however, prospective studies are needed to determine the effects of steroid use on the outcomes of other cancers. In lung cancer, the use of ≥10 mg of prednisone equivalent upfront has been associated with poorer outcome, but the irAEs were not the only indications for steroid use (common indications were dyspnoea, fatigue and brain metastases).[258] Two different situations could be considered based on these results; if steroids are used before commencing ICIs for cancer-related indications, a dose >10mg/day may be deleterious[258], whereas no deleterious effect has been demonstrated so far for the use of steroids for irAE treatment. Interestingly, progression-free survival was longer in patients with urothelial cancers who developed irAE than those who did not, and this benefit was not altered by steroid use[259].

Despite those trials showing no effect on cancer outcomes with irAE treatment, other studies have suggested that caution is needed. For example, glucocorticoids have been suggested to promote breast cancer metastasis[260] through activation of the glucocorticoid receptor. In addition, another study has suggested that clinically-relevant doses of infliximab only had a minor influence on the activity of tumour-specific T-cells in vitro, whereas even low doses of corticosteroids markedly impaired the antitumour activity of tumour-specific T cells.[261]

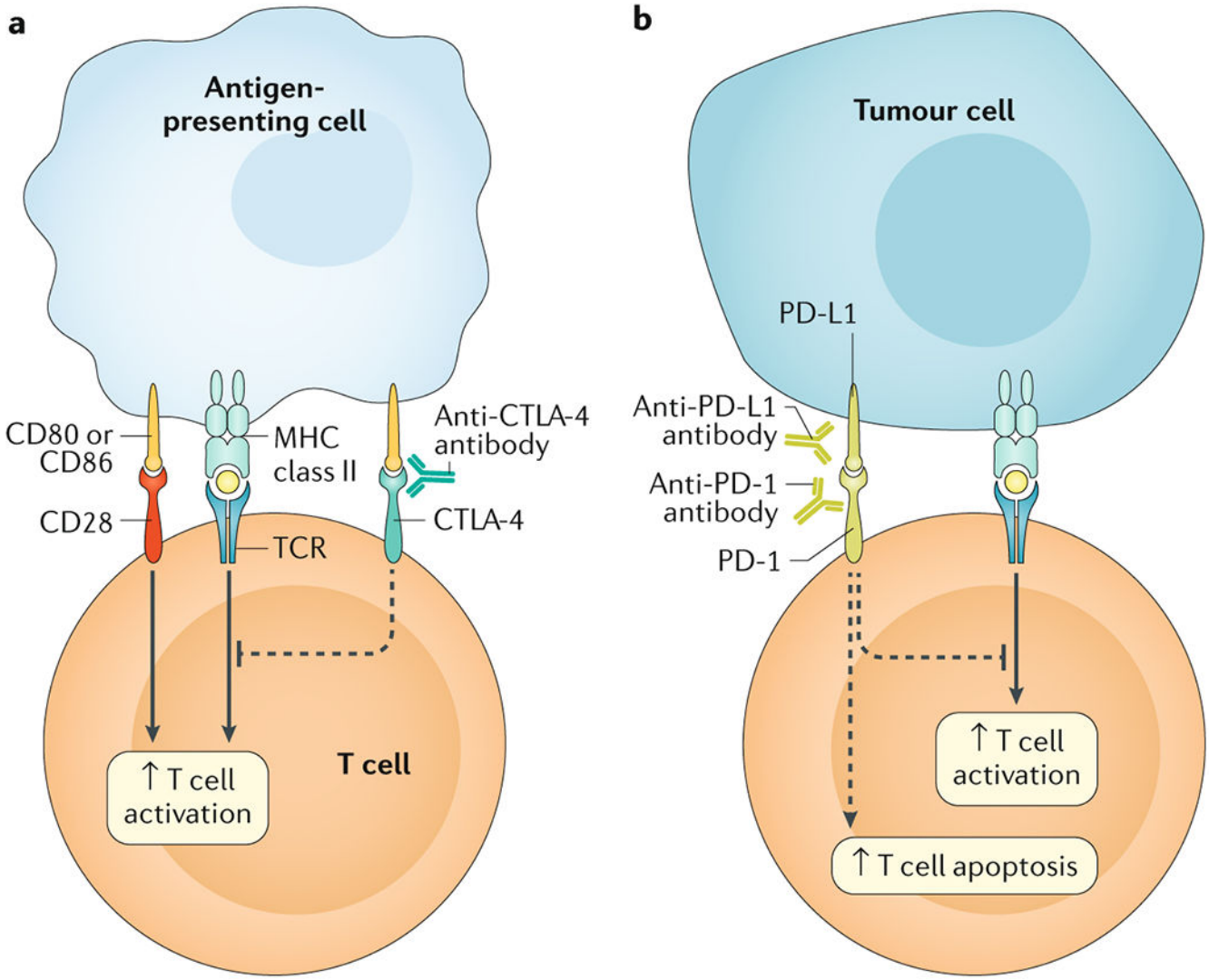

Figure 1. Mechanism of immune checkpoints and ICIs.

The main immunotherapy approaches that are approved for clinical use in cancer are the immune checkpoint inhibitors (ICIs). These therapies are monoclonal antibodies that target the receptors CTLA-4 and PD-1 and the PD-1 ligand, PD-L1, which are involved in the regulation of T cell activation. A| T cell activation requires two signals: first, antigen recognition by the T cell receptor (TCR) following antigen presentation by major histocompatibility complex (MHC) class II molecules on the surface of antigen-presenting cells and, second, signal modulation by CD80 or CD86 binding to the CD28 receptor. CTLA-4 is located on the T-cell surface and competes with the CD28 receptor to bind CD80 or CD86, thereby blocking T cell activation. CTLA-4 inhibitors block CTLA-4–CD80 or CTLA-4–CD86 binding to facilitate T cell activation (dashed line). B| PD-1 is a surface receptor that is expressed by T-cells and promotes apoptosis of antigen-specific T-cells and reduces apoptosis of regulatory T-cells [252,253] through its interaction with its ligand PD-L1, which is expressed by tumour cells and myeloid cells. This interaction is useful in preventing autoimmunity in physiological conditions, but cancer cells exploit this process to

escape from immune system activity upregulating PD-L1 expression.[254,255] PD-1 and PD-L1 inhibitors block the PD-1–PD-L1 interaction, facilitating T cell activation and survival (dashed lines).

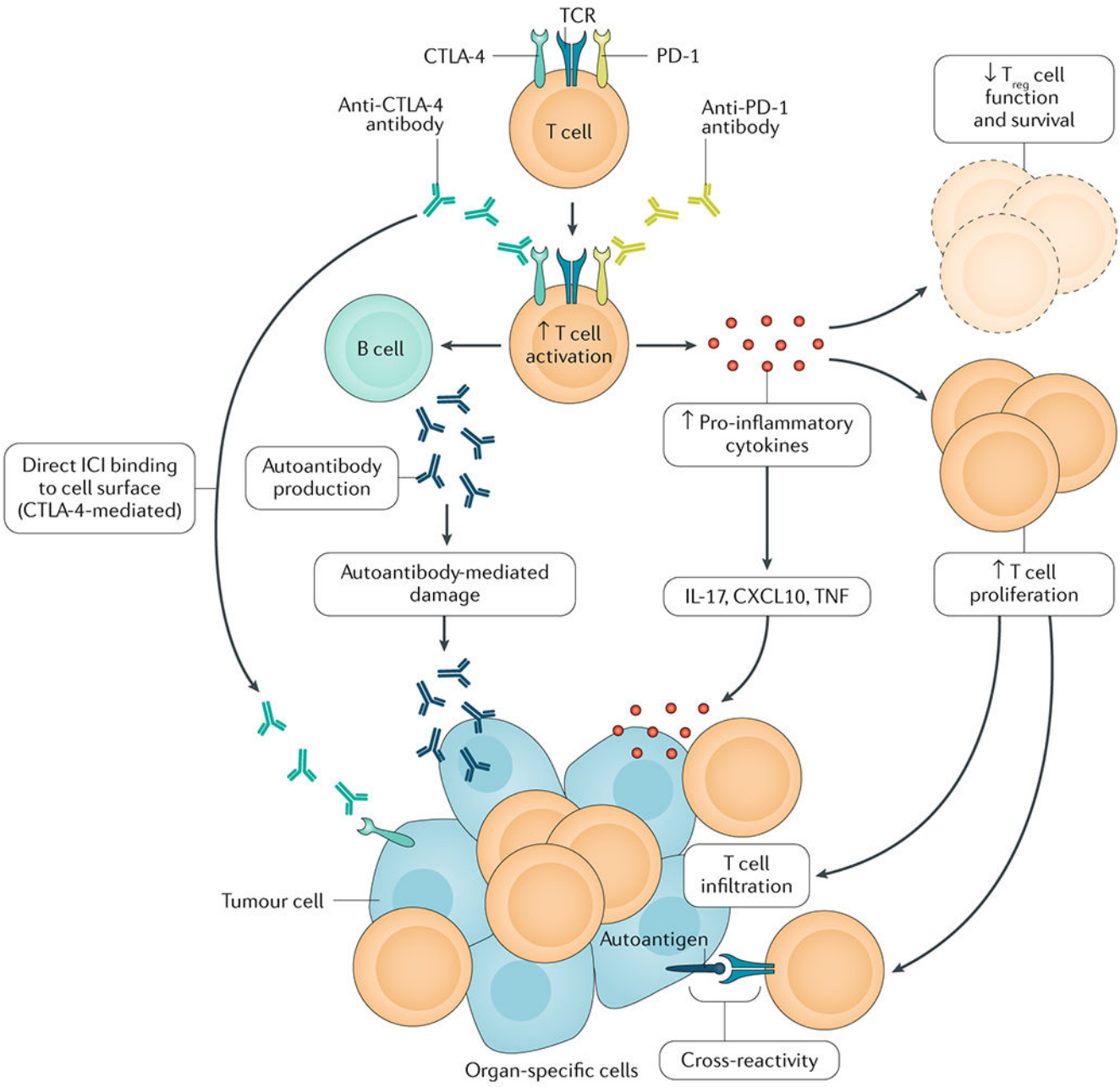

Figure 2. Mechanism of irAE.

The mechanisms of immune-related adverse events (irAE) owing to immune checkpoint inhibitors (ICIs) depend on the type of ICI therapy used (anti-PD-1 or anti-PD-L1 inhibitors versus anti-CTLA-4 inhibitors). CTLA-4 inhibitors can induce several cellular alterations, such as T cell activation and proliferation, impaired regulatory T cell (T_{reg}) survival and increased levels of T_H17 cells, in addition to the induction of cross-reactivity between antitumour T cells and antigens on healthy cells and autoantibody production. PD-1 and PD-L1 inhibitors lead to a reduction in T_{reg} survival and T_{reg} inhibitory function and increase cytokine production. TCR, T cell receptor.

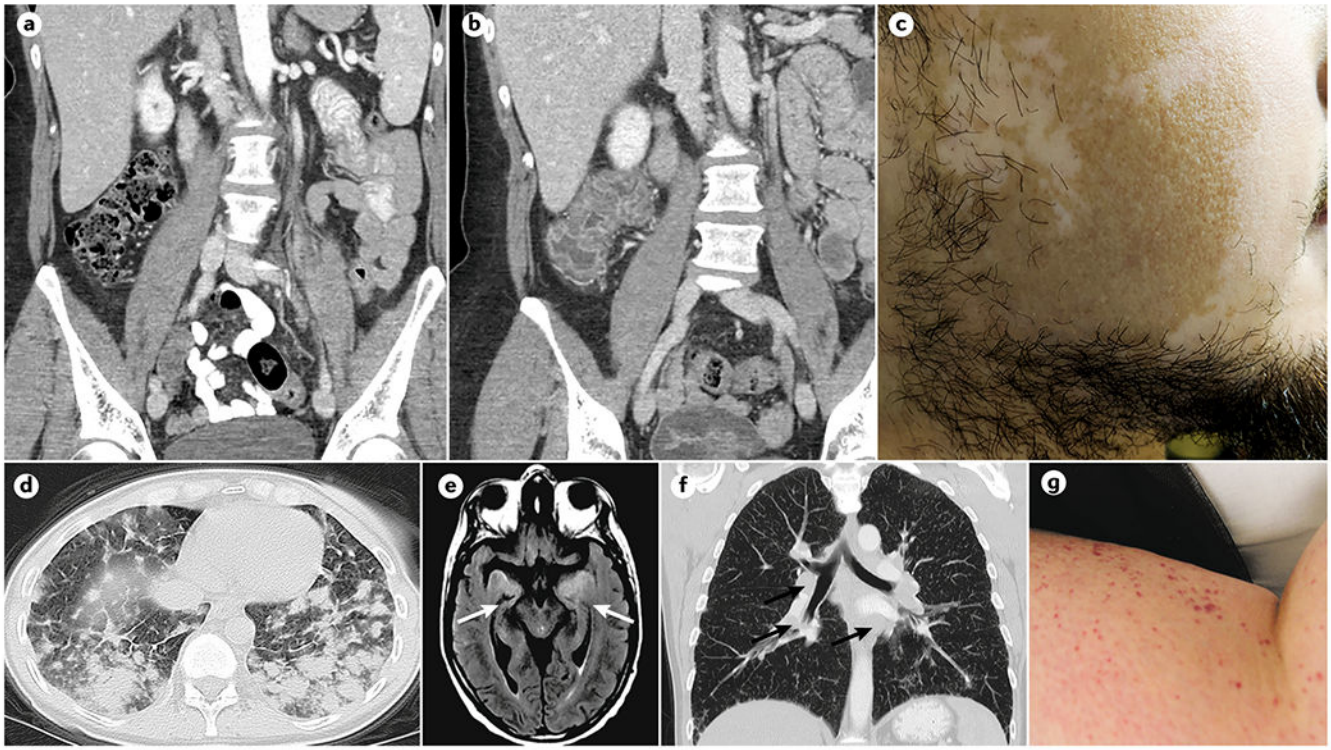

Figure 3. Common radiological and/or photographical appearance of irAEs.

A| CT image of immune checkpoint inhibitor (ICI)-associated before the onset of immune related colitis. B| CT image of ICI-associated colitis after colitis onset. C| Vitiligo. D| High-resolution pulmonary CT showing interstitial lung disease of ICI-associated pneumonitis. E| MRI with T2 flair of ICI-associated encephalitis; an abnormal signal can be observed bilaterally in the insula and medial temporal lobes. The patient presented with new-onset confusion and weakness whilst using anti PD-1 therapy. F| Pulmonary CT showing multiple hilar adenopathy in a patient with sarcoidosis after ipilimumab treatment. Biopsy of an adenopathy demonstrated non-caseating granulomas. G| Cutaneous purpura in a patient treated with nivolumab.

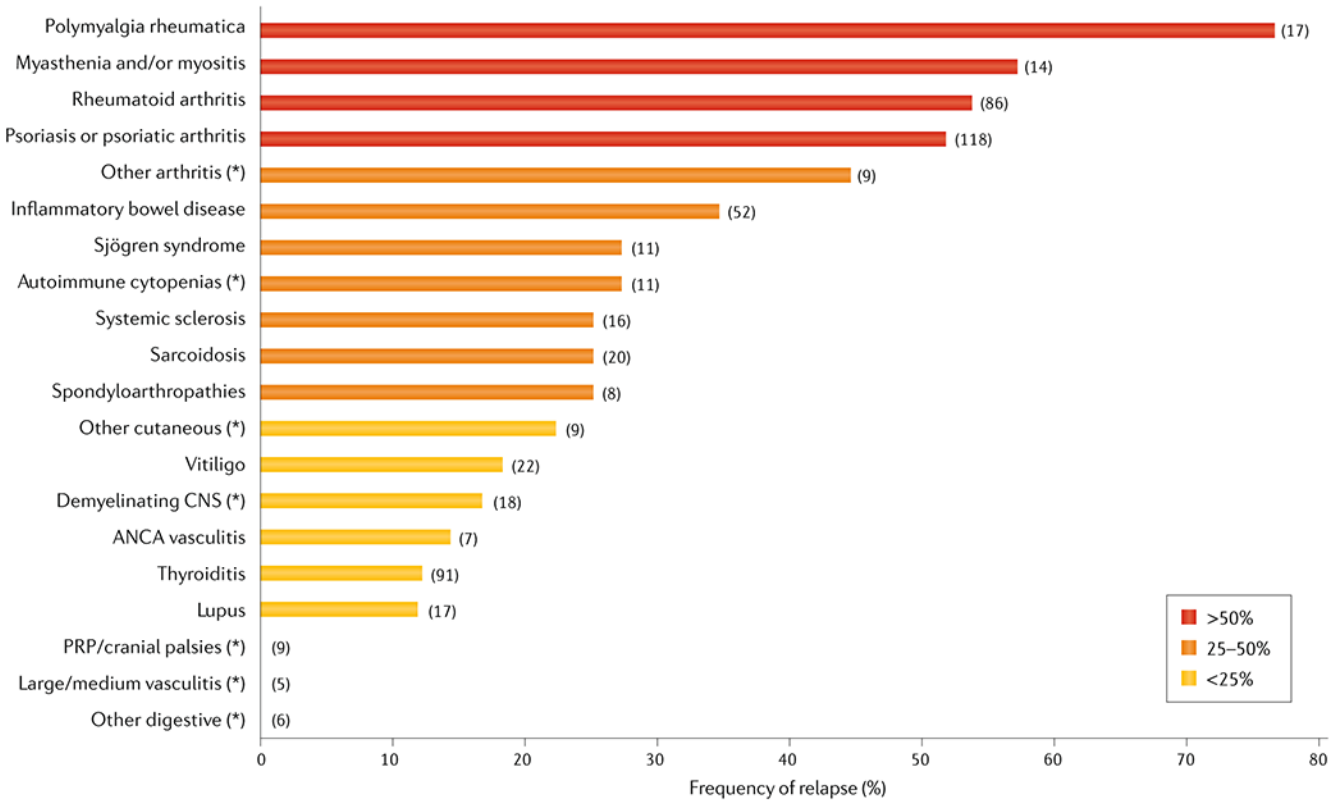

Figure 4.

Rate of reactivation/flare of pre-existing autoimmune diseases after ICI therapy.

We searched MEDLINE for articles published until January 1st 2020 using the terms “pre-existing (preexisting)” and “autoimmune” in combination with “checkpoint”, ”CTLA-4”, ”PD-1” and “PD-L1”, with no search restrictions. Study designs were considered in the following order (listed from highest to lowest evidence quality): systematic reviews, controlled trials, prospective cohort studies, case-control studies, retrospective studies and case series. The following relevant information was defined as selection criteria: a well-defined “population at risk” (patients diagnosed with an autoimmune disease before the initiation of the ICI therapy), available information to calculate the rate of relapse (patients who relapsed/total number of patients exposed to the drug, to be calculated for every different type of underlying autoimmune disease), and whether the relapse was linked to the underlying autoimmune disease or not. Duplicate publications, case reports, experimental studies and articles including incomplete/irrelevant information were excluded. We also manually searched the reference list of relevant articles retrieved and the EMBASE database. The following Figure shows a flow diagram of our search results. The available information about the use of immune checkpoint inhibitors was extracted from nine studies including patients with cancer and pre-existing autoimmune diseases[150,151,153–159]. Rates of reactivation/flare were defined as “number of patients who relapsed/total number of patients exposed to the drug”, to be calculated for each underlying autoimmune disease. Rates in individual diseases or grouped diseases with at least 5 treated individuals are represented in this Figure. For more detailed information about the

methodology and rates for each individual autoimmune disease, see the Supplementary Material.

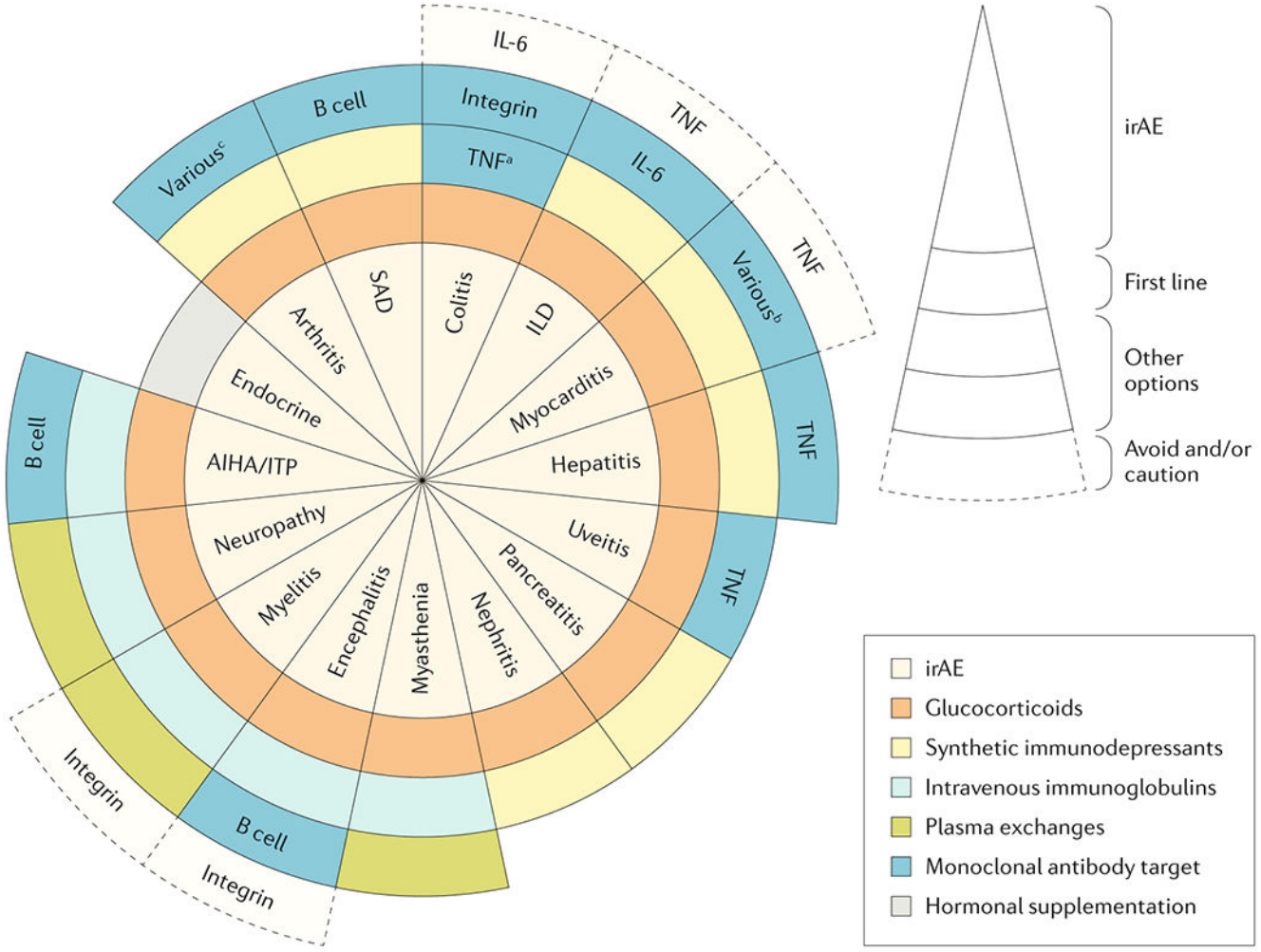

Figure 5.

Suggested therapeutic algorithm for the organ-by-organ management of irAEs. When a systemic therapy is considered in patients presenting with immune-related adverse events owing to immune checkpoint inhibitors (irAEs), the first-line treatment are glucocorticoids with the exception of adverse effects that affect the endocrine system. Other therapies to be considered in severe/refractory cases depend on the affected organ system but can include synthetic immunosuppressants, intravenous immunoglobulin (IVIG), plasma exchange and monoclonal antibodies. These therapeutic suggestions are based on recommendations included in official guidelines, data from some retrospective studies, isolated published cases and personal experience of the authors. SAD: systemic autoimmune diseases; ILD: interstitial lung disease. [a]Avoid etanercept owing to the risk of autoimmune inflammatory colitis; [b] consider abatacept or alemtuzumab; [c] consider infliximab or tocilizumab.