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REVIEW ARTICLE

Diagnosis, monitoring, and management of adverse events from immune checkpoint inhibitor therapy

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ABSTRACT

Immune checkpoint inhibitor therapy (ICIT) is now a standard of care for a variety of cancers in both the metastatic and adjuvant settings. As a result, an understanding of the timing, epidemiology, monitoring, diagnosis, and management of immune-related adverse events (irAEs) associated with ICIT is imperative. This article reviews specific irAEs by organ system, consolidating recommendations from multiple guidelines and incorporating data from case reports to highlight additional evolving therapeutic options for patients. Managing irAEs requires early recognition, early intervention, and education of the patients and the multidisciplinary health care team alike. Given the durable responses observed with ICIT, and the irreversible nature of some of the irAEs, further research into management of the sequelae of ICIT is required.

Key Words Immune checkpoint inhibitors, adverse events, PD-L1, PD-1, CTLA-4, immunotherapy

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INTRODUCTION

In 2011, the U.S. Food and Drug Administration approved ipilimumab, an inhibitor of CTLA-4, for use in metastatic melanoma. That authorization heralded the arrival of a wave of immune checkpoint inhibitor therapy (ICIT) for use in treating various malignancies. Research into, and use of, ICIT has grown exponentially, with global sales of ICIT agents expected to exceed US$25 billion by the year 2022[1]. However, as the use of those medications increases, so too do adverse events.

Given that the mechanism of action of ICIT differs substantially from traditional cytotoxic therapies and from targeted molecules alike, it is critical that all physicians caring for cancer patients build their awareness of the related adverse events. Early recognition and management of adverse events is paramount to improving outcomes for patients facing those potentially life-threatening complications[2]. To that end, detailed guidelines for adverse effect management were created by leading authorities, including the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO)[3,4]. In the present review article, we aim to highlight broad principles concerning the recognition and management of immunotherapy-related adverse events (irAEs), before briefly reviewing specific complications by organ system.

REVIEW

Biology, Epidemiology, and Monitoring of irAEs

The current targets of funded ICIT are CTLA-4, PD-1, and PD-L1, each of which function to inactivate or suppress T cell activity[5]. Thus, the adverse effects associated with immunotherapy are generally inflammatory in nature, as a consequence of uninhibited T cells acting against normally functioning cells[6]. However, despite similarities in clinical manifestations, emerging data suggest immunologic differences between irAEs and "traditional" autoimmune diseases, because conventional autoantibodies are often not detectable when irAEs are diagnosed[7].

The prevalence of irAEs is high, with reported rates of up to 90% after treatment with a CTLA-4 inhibitor and up to 70% after treatment with a PD-1/-L1 inhibitor[8]. The rates of grade 3 or greater toxicities reported with ipilimumab (a CTLA-4 inhibitor) in phase III clinical trials approach 50%[9]. Grade 3 or greater toxicities for PD-1/-L1 inhibitor therapies have been less frequently reported, but have occurred in approximately 10%–15% of patients[10]. Compared with

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monotherapy, combination immune checkpoint blockade is associated with increased rates of high-grade dermatologic, gastrointestinal, and hepatic toxicities[11].

Timing of irAEs

Most irAEs occur within 3 months of ICIT initiation, although early dermatologic irAEs have been reported within 24 hours of treatment initiation[4]. In contrast, late irAEs can occur more than 1 year into treatment and have been reported months or even years after discontinuation of therapy[12,13]. Table I summarizes the median timing for onset of selected irAEs[4,14]. Overall, it is important to maintain a high degree of suspicion for irAEs when investigating new symptoms that a patient is experiencing at any time during and after therapy.

Routine Monitoring

Although the diagnosis of many irAEs (especially dermatologic and gastrointestinal toxicities) is clinical, other toxicities can be detected early with the routine use of laboratory testing. The Toxicity Management Working Group of the Society for Immunotherapy of Cancer recommends that, before ICIT is started, a complete blood count, metabolic panel, thyroid testing, hemoglobin A1c, creatine kinase, and infection work-up for hepatitis, human immunodeficiency virus, and cytomegalovirus be obtained[15]. The Society also recommends a baseline electrocardiogram and measurement of troponin, with consideration of a baseline pulmonary function test (patients with pre-existing pulmonary disease), morning serum cortisol and adrenocorticotropic hormone (patients with pre-existing endocrine disease), and serum brain natriuretic peptide (patients with pre-existing cardiac disease). Similarly, the ASCO guideline recommends an electrocardiogram and consideration of serum troponin at baseline in patients treated with combination therapy, although they note a lack of clear evidence supporting the value or efficacy of that strategy[3]. The ESMO guideline recommends laboratory testing before each cycle of therapy, including thyroid function testing [triiodothyronine, free thyroxine (T4), and thyroid-stimulating hormone (TSH)], hepatic transaminases, bilirubin, creatinine, and urea[4]. For infusions delivered every 2 weeks, the frequency of thyroid testing can, after 3 months, be reduced to every 2nd cycle. The ASCO guideline also recommends monitoring thyroid tests (TSH, free T4) every 4–6 weeks, serum creatinine before every dose, and serum glucose with each cycle for 12 weeks, followed by monitoring every 3–6 weeks[3].

Management Principles for irAEs

Holding or Discontinuing Immune Checkpoint Blockade

For most grade 1 toxicities, therapy continues, with close monitoring of the patient being required. However, for certain grade 1 irAEs, including cardiac, neurologic, or renal complications, holding ICIT might be considered, although guidelines vary about when a hold is required[3,4]. Therapy might also be held while hormone levels are being stabilized in endocrine toxicities such as adrenal insufficiency, thyroid dysfunction, or hypophysitis.

For grade 2 irAEs, immune checkpoint inhibitors should generally be held while treatment for the complication is initiated. After a patient experiences a grade 3 or greater irAE, ICIT should usually be discontinued[3,4].

Immunosuppressive Therapy

Corticosteroid use is the backbone of treatment for most irAEs, and high-dose therapy—usually prednisone or methylprednisolone 1–2 mg/kg daily—should be started early when an irAE is suspected[3,4,6]. Lower doses of corticosteroids (prednisone or equivalent 10–30 mg daily) are recommended as the initial treatment for rheumatologic irAEs; higher doses have been used for cardiovascular or neurologic toxicities[4,16]. Corticosteroid therapy must be monitored carefully, particularly in older adults, who have a higher risk of complications such as delirium, and in patients with diabetes or heart disease[17].

If improvement is not noted with corticosteroids, further immunosuppressive therapy is recommended. Depending on the organ system involved, treatments that have been used include infliximab, azathioprine, mycophenolate, tacrolimus, cyclosporine, rituximab, plasmapheresis, and anti-thymocyte globulin[4,18–20].

Use of ICIT in Patients with Autoimmune Diseases and in Transplant Recipients

Because of the risk of exacerbating pre-existing autoimmune conditions in patients with autoimmune diseases and in patients who have undergone transplantation, data concerning use of ICIT in those populations are sparse[21]. Nevertheless, as the use of ICIT expands, real-world evidence to help guide ICIT in patients with pre-existing autoimmune disease is emerging.

Abdel-Wahab *et al.*[22] recently completed a systematic review on this topic. The most common pre-existing condition was psoriasis or psoriatic arthritis (22.8%), followed

TABLE I Approximate timing of onset for selected immunotherapy-related adverse events

Organ system	Single-agent inhibitor		Combination inhibitors
	CTLA-4 (ipilimumab)[14]	PD-1 (nivolumab)[4]	CTLA-4 and PD-1 (ipilimumab–nivolumab)[4]
Dermatologic	3–10 Weeks	20 Weeks (range: 1.3–50.9 weeks)	5.6 Weeks (range: 0.1–55.0 weeks)
Hepatic	7–14 Weeks	14 Weeks (range: 1.9–25.1 weeks)	7.4 Weeks (range: 2.1–48.0 weeks)
Gastrointestinal	5–10 Weeks	26.3 Weeks (range: 13.1–57.0 weeks)	7.4 Weeks (range: 1.0–48.9 weeks)

by rheumatoid arthritis (16.3%) and inflammatory bowel disease (10.6%). Nearly half the patients included (46.2%) had active autoimmune disease when ICIT was started. Exacerbation of pre-existing autoimmune conditions was reported in 50% of patients, and 34% developed new irAEs unrelated to their pre-existing condition. However, most exacerbations were managed and did not require treatment discontinuation. Other recent retrospective studies support those findings, reporting that toxicities from ICIT are generally manageable in patients with pre-existing autoimmune conditions[23]. Overall, in the absence of larger prospective studies, the risks and benefits of ICIT should be reviewed on an individual basis with patients, considering the type and severity of their pre-existing condition or conditions. While on therapy, patients should be carefully monitored (in a multidisciplinary setting if possible) for exacerbation of any pre-existing diseases.

The data for the use of ICIT in transplant recipients is even more sparse. Immune checkpoint inhibitors appear to be tolerated by patients who have undergone stem-cell transplantation and transplantation of some solid organs, but cases of graft-versus-host disease and solid-organ graft rejection—including kidney and heart grafts—have occurred[23]. Overall, although ICIT can be safe and effective for patients who have undergone transplantation, it should be used cautiously and with the help of a multidisciplinary team. Additionally, patients have to be well-informed about the risks associated with treatment.

Relationship Between irAEs and the Efficacy of ICIT

Emerging data suggest a possible association between the development of adverse events with ICIT and the efficacy of treatment. Retrospective data showed improved outcomes in patients with lung cancer who developed irAEs compared with patients who did not[24]. Ricciuti *et al.*[25] conducted a multicentre retrospective study in patients with advanced non-small-cell lung cancer and found a median overall survival of 17.8 months when an irAE developed, compared with 4.0 months when no irAE occurred; interestingly, overall survival significantly improved in patients who experienced 2 or more irAEs (26.8 months) compared with those who experienced 1 irAE (11.9 months) or no irAEs (4.0 months). Similarly, the occurrence of colitis and vitiligo in patients with melanoma is also associated with improved survival outcomes[26].

The effect that treating irAEs has on ICIT efficacy is a controversial subject. Although one report found that inferior outcomes were associated with high-dose corticosteroid therapy use for hypophysitis, other studies in melanoma suggested no detrimental effect when treating irAEs[27]. Guidelines currently recommend that the corticosteroid dose be tapered (usually over a minimum of 4 weeks) to as low a dose as possible[3,28]. Data concerning the effect of other immunosuppressive therapies on the efficacy of cancer treatment are very limited[15].

Management of irAEs by Organ System

Dermatologic irAEs

Immune checkpoint inhibitors are associated with a number of dermatologic adverse events, including vitiligo (occurring almost exclusively in patients with melanoma, although cases of vitiligo with other malignancies have been reported)[29], inflammatory dermatitis, psoriasis, bullous diseases, and severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens–Johnson syndrome)[3,4]. For patients treated with PD-1 inhibitors, the reported incidence of rash is approximately 15%; pruritus, up to 20%; and vitiligo, less than 10%[30]. Table II summarizes the ASCO and ESMO guideline recommendations for dermatologic irAEs[3,4].

In severe cases or in those refractory to steroid therapy, additional therapeutic options depend on the type of lesion. For bullous pemphigoid lesions, tetracycline antibiotics, niacinamide, and rituximab have been used[3,31], and Ridpath *et al.*[32] also described a case in which the patient responded to combination plasma exchange and rituximab. In case reports of toxic epidermal necrolysis or Stevens–Johnson syndrome, cyclosporine therapy has shown efficacy, and other reported options include intravenous immunoglobulin, tacrolimus, or infliximab[33,34].

Gastrointestinal irAEs

Diarrhea occurs in up to 54% of patients treated with CTLA-4 inhibitors, with colitis being discovered on colonoscopy in up to 22% of cases[35]. In PD-1 inhibition, rates are lower, with diarrhea being reported in approximately 20% of patients, and grade 3 or greater toxicity being reported in 1%–2%. In combination therapy, the incidence of diarrhea is increased, but rates of colitis are similar to those receiving monotherapy with ipilimumab (CTLA-4 inhibitor)[4].

For grade 1 diarrhea (defined as fewer than 4 liquid stools daily above baseline, or a mild increase in ostomy output), patients should be carefully monitored for volume depletion while immunotherapy is continued[3,4]. It is important to rule out other causes for the diarrhea, with an appropriate infection work-up, including testing for *Clostridium difficile*[35].

For grade 2 toxicity (defined as presence of blood, nocturnal stools, abdominal pain, or 4–6 stools daily above baseline), immunotherapy should be held temporarily, and systemic corticosteroid therapy (1–2 mg/kg) should be initiated without waiting for colonoscopy[3,4]. Escalation of steroid dosing to 2 mg/kg daily in refractory cases could be considered, followed by a slow taper over at least 4 weeks[19].

For patients with grade 3 or greater toxicity, inpatient treatment is recommended, beginning with intravenous steroid therapy. If no improvement occurs within 48–72 hours, or if symptoms continue to deteriorate[4], initiation of infliximab can follow (at a dose of 5 mg/kg, which can be repeated after 2 weeks). For cases refractory to infliximab, the α4β7 integrin–targeted antibody vedolizumab has shown efficacy and has a reasonable safety profile[36]. Cytomegalovirus reactivation has been associated with immunotherapy-induced colitis not responding to steroids or infliximab, making repeat diagnostic testing paramount in treatment-refractory cases[37].

Hepatic irAEs

Hepatotoxicity from immune checkpoint inhibitors occurs in up to 10% of patients treated with monotherapy and in up to 30% of patients treated with combination therapy[4]. All

TABLE II Management recommendations for dermatologic toxicity from immune checkpoint inhibitor therapy (ICIT)

Toxicity grade	Definition
1	Symptoms not affecting quality of life, or lesions covering less than 10% of body surface area, without erythema *ASCO and ESMO recommendations* • Topical emollients • Mild-to-moderate topical corticosteroid daily • Continue ICIT
2	Symptoms affecting quality of life, including lesions covering 10%–30% of body surface area, without meeting criteria for grade 3 or 4 toxicity *ASCO recommendations* • Topical antihistamine therapy • Medium- to high-potency topical steroid therapy • Systemic corticosteroid therapy could be considered (prednisone equivalent 1 mg/kg daily) • Consider holding ICIT until symptoms improve to grade 1 *ESMO recommendations* • Twice-daily topical steroid use (moderate-to-potent strength) • Oral or topical antihistamine therapy • Continue ICIT • Consider dermatology referral
3	Symptoms present as skin sloughing, or lesions involving more than 30% of body surface area, with associated pain and effect on activities of daily living or failure to respond to therapy for grade 2 toxicity *ASCO recommendations* • Hold ICIT • Consult dermatology • Topical emollients • Oral antihistamine therapy • High-potency topical steroid therapy • Methylprednisolone 1–2 mg/kg (or equivalent), tapering over 4 or more weeks • Consider rituximab for bullous pemphigoid • Restart ICIT after consultation with dermatologist *ESMO recommendations* • Hold ICIT • Potent topical steroid therapy • For mild symptoms, use oral corticosteroid (for example, prednisone or equivalent 0.5–1 mg/kg), and wean over 1–2 weeks • For severe symptoms, use intravenous methylprednisolone 0.5–1 mg/kg (or equivalent), and wean over 2–4 weeks • Restart ICIT after discussion with dermatologist and symptoms improved to grade 1 or mild grade 2
4	Symptoms present as intolerable or severe rashes unmanageable with grades 1–3 interventions, or blistering involving more than 30% of body surface area, with associated fluid or electrolyte abnormalities *ASCO recommendations* • Discontinue ICIT • Admit patient to hospital with urgent dermatology consultation • Intravenous methylprednisolone 1–2 mg/kg (or equivalent) • Consider infectious disease consultation if secondary cellulitis is suspected, or other infectious risk factors are present *ESMO recommendations* • Discontinue ICIT • Urgent dermatology assessment with biopsy • Intravenous methylprednisolone 1–2 mg/kg (or equivalent)

patients treated with ICIT should be aware of the symptoms of liver dysfunction, and transaminase and bilirubin levels should be regularly monitored.

For grade 1 toxicity, ICIT can be continued while transaminase levels are monitored. Ruling out other possible causes for hepatitis—including supplements, alcohol, over-the-counter medications, and viral infections—is critical[4,15].

In the setting of grade 2 hepatic toxicity, immunotherapy should be held, and systemic corticosteroid therapy should be started if laboratory parameters do not improve within 3–7 days[3,4].

In the setting of grade 3 or 4 toxicity, immunotherapy should be discontinued, and corticosteroid therapy initiated immediately. If liver enzymes continue to worsen, the ASCO and the ESMO guidelines both recommend therapy with mycophenolate mofetil 500–1000 mg twice daily, based on case reports of successful therapy[3,4]. Other treatment options attempted in refractory cases include antithymocyte globulin, tacrolimus, and cyclosporine[38–40].

Pulmonary irAEs

The incidence of pneumonitis is higher with PD-1 than with CTLA-4 inhibitor therapy[4]. Additionally, pneumonitis is more common with PD-1 inhibitor therapy (approximately 3%–4%) than with PD-L1 inhibition (1%–2%). Pneumonitis is diagnosed in up to 10% of patients treated with combination immune checkpoint inhibitors, although dyspnea and cough are seen in up to 40% of patients[4]. Diagnostic work-up should include computed tomography imaging and chest radiography.

For grade 1 toxicity, ICIT should be delayed while a work-up to rule out other causes, including infection, is completed[3,4].

For grade 2 toxicity, empiric antibiotics, corticosteroids, and respirology consultation for bronchoscopy should be considered. Immunotherapy should be held until the steroid dose has been successfully tapered to less than 10 mg prednisone or equivalent daily.

Grade 3 or 4 toxicities necessitate hospital admission, intravenous corticosteroid therapy, empiric antibiotic therapy, and respirology or infectious disease service consultation (or both)[3,4]. In refractory cases, treatments including infliximab, cyclophosphamide, and mycophenolate have been reported[41].

Endocrine irAEs

Immune checkpoint inhibitors are associated with several endocrine toxicities, including thyroid dysfunction, hypophysitis, adrenal insufficiency, and new-onset

diabetes[4]. The most frequent of those adverse effects are acute hypophysitis (resulting in several possible central endocrine deficiencies, including hypothyroidism, adrenal insufficiency, diabetes insipidus, and hypogonadotropic hypogonadism) and thyroid gland dysfunction[3,15]. Hypophysitis commonly occurs with use of anti–CTLA-4 antibodies; reported rates vary significantly between 0% and 17%. Rates of less than 13% are reported with combination immune checkpoint inhibition[3]. Thyroid dysfunction is reported in between 5% and 20% of patients treated with immune checkpoint inhibitors; it appears to occur more frequently in patients treated with anti–PD-1 or anti–PD-L1 antibodies[3,4,15].

A meta-analysis of randomized controlled trials[11] found that, compared with monotherapy, combination immune checkpoint blockade was associated with significantly increased risks for endocrine toxicity (hazard ratios: 2.84 for hyperthyroidism, 1.71 for hypothyroidism, and 4.24 for hypophysitis). However, when considering only high-grade endocrine toxicity, no statistically significant differences were found for combination therapy or monotherapy compared with immune checkpoint inhibitors.

Management of grade 1 thyroid dysfunction requires close monitoring of serum TSH and free T4 to ascertain whether the finding persists. For hypothyroidism, replacement therapy is commenced only if the patient develops symptoms or if the finding persists (serum TSH > 10 mIU/L) for more than 1 cycle[3,4,15].

For higher-grade thyroid dysfunction, immunotherapy should be held until symptoms resolve, and endocrinology consultation is advised. Inpatient admission and intravenous therapy for hypothyroidism might be required for severe symptoms or if signs of myxedema (such as low heart rate or hypothermia) are present[3]. Management of higher-grade hyperthyroidism includes nonselective beta-blockade, hydration, and consideration of corticosteroid therapy (prednisone 1–2 mg/kg daily, tapered over approximately 2 weeks), iodine, or other medications such as methimazole or propylthiouracil[3,4].

The work-up for hypophysitis should include magnetic resonance imaging (MRI) of the brain with a pituitary-specific protocol[4]. Required bloodwork (which should be ordered before steroid therapy is initiated) includes morning cortisol, adrenocorticotropic hormone, TSH, free T4, luteinizing hormone, follicular stimulating hormone, testosterone or estradiol, insulin-like growth factor 1, and prolactin[4,15]. Management of hypophysitis consists primarily of corticosteroid therapy (orally for moderate symptoms, intravenously for severe symptoms of mass effect or hypoadrenalism), with replacement of other hormones based on laboratory testing and patient symptoms[3]. With respect to the decision to continue immunotherapy, guidelines differ. The ESMO guideline recommends continuing treatment if the patient is asymptomatic or exhibiting only vague symptoms; the ASCO guideline recommends considering holding ICIT until the patient is stabilized on hormone replacement therapy[3,4]. In cases of combined adrenal and thyroid insufficiency, it is of particular importance that corticosteroids be started several days before thyroid hormone replacement is initiated, to prevent precipitating an adrenal (Addisonian) crisis[3,15].

Other endocrine toxicities are relatively rare, and endocrinology consultation is advised to assist with management. Often, a lifelong requirement for one, some, or all of thyroid, adrenal, and insulin replacement therapy emerges after an immunotherapy complication—something that cannot be predicted at the time of diagnosis. The role of immunosuppressive therapy in decreasing the duration or severity of symptoms is not established[4].

Neurologic irAEs

Neurologic complications of ICIT are relatively rare, but their severity and potential lethality mandate careful surveillance[42]. These irAEs can also correlate with myositis and cardiac toxicity[43]. Neurologic complications are commonly reported to occur in 1%–4% of patients, but one recent publication suggested a rate as high as 6% with anti–PD-1 therapy and up to 12% in patients receiving combination therapy[4]. Grade 3 or greater toxicities occur in less than 1% of patients[42]. A variety of neurologic complications are associated with immune checkpoint blockade, including Guillain–Barré syndrome (GBS), transverse myelitis, encephalitis, polyneuropathy, aseptic meningitis, and myasthenia gravis[42].

Myasthenia gravis is one of the more commonly reported neurologic toxicities associated with ICIT, occurring *de novo* or as an exacerbation of pre-existing (sometimes subclinical) disease. Most cases of myasthenia gravis respond to treatment, but one case series reported a myasthenia gravis–specific mortality rate of 30.4%, highlighting the severity of the complication[44]. Treatment for myasthenia gravis consists of corticosteroids (prednisone 1–2 mg/kg daily) in combination with pyridostigmine (30 mg 3 times daily, gradually increasing to 120 mg 4 times daily), with consideration of intravenous immunoglobulin (2 g/kg over 5 days) or plasma exchange for severe cases[3,44]. Phadke *et al.*[45] reported a case in a patient with a previously known history of autoantibody-positive myasthenia gravis treated with pembrolizumab, whose treatment also included 4 doses of rituximab. The patient's symptoms improved after 1 week, although the patient ultimately died from an aspiration pneumonia 1 month later.

Work-up for the rarely reported but very serious—and sometimes fatal—GBS toxicity associated with ICIT[4] (often presenting with sensory polyneuropathy followed by symmetric muscle weakness and hyporeflexia) should include MRI of the spine, assessment of antiganglioside antibodies (for example, GQ1b), nerve conduction studies, pulmonary function testing (including maximum inspiratory and expiratory pressures), and lumbar puncture (including cytology)[3,4,15]. Immune checkpoint inhibitors should be discontinued immediately, and the patient should be admitted to hospital. Unlike idiopathic GBS, for which steroids are not routinely used, a trial of intravenous steroids (methylprednisolone or equivalent 2 mg/kg daily or 1000 mg daily for severe symptoms) is recommended for immunotherapy-related GBS[3,42]. In addition, management should include intravenous immunoglobulin or plasma-exchange therapy. Careful monitoring of respiratory status is critical in cases of GBS, as is assessment for autonomic dysfunction. Chronic inflammatory demyelinating polyneuropathy might occur after an acute episode, but its incidence appears to be extremely infrequent[42].

Transverse myelitis is a debilitating potential complication of ICIT. Guidelines for work-up recommend MRI of the spine, lumbar puncture, and bloodwork (including testing for other potential causes such as HIV, vitamin B_{12} deficiency, and syphilis, among others). Management includes discontinuation of ICIT, neurology consultation, high-dose corticosteroid therapy (methylprednisolone 1000 mg daily or equivalent for 3–5 days, then 2 mg/kg daily), and intravenous immunoglobulin therapy or plasma exchange[3,4]. Other reported treatments include cyclophosphamide, and one case report described successful therapy of immune checkpoint inhibitor–related transverse myelitis with infliximab[46].

For other neurologic irAEs, management should include neurologic consultation, consideration of steroid therapy, and appropriate testing to rule out other causes, including malignant progression, paraneoplastic phenomena, and infections[3,4,15].

Musculoskeletal and Rheumatologic irAEs

Relative to other neuromuscular toxicities of immune checkpoint blockade, myositis is more often reported. Myositis most commonly presents with mild myalgias, but in more severe cases, presentations can be similar to dermatomyositis and necrotizing autoimmune myopathy. Other cases describe overlap with GBS or myasthenia gravis[43]. A distinguishing characteristic of immune-related myositis, in contrast to typical myositis, is a predilection for ocular involvement[42]. Notably, cardiac involvement (myocarditis) was reported in approximately 30%–35% of myositis cases, and most reported cases of fatal myositis had either cardiac or diaphragmatic involvement[42,43].

Work-up should include serum creatine kinase, C-reactive protein, erythrocyte sedimentation rate, and troponin (with further cardiac imaging, if required), plus consideration of electromyography and MRI if the diagnosis is uncertain[3]. Immunotherapy should be held for symptoms of grade 2 severity or higher (moderate weakness causing limitations in instrumental activities of daily living). Treatment includes nonsteroidal anti-inflammatory drugs, and oral corticosteroid therapy (prednisone 0.5–1 mg/kg daily)[3,15]. Most cases of myositis respond well to corticosteroid therapy, but in refractory or severe cases, other treatment options include intravenous immunoglobulin or plasma exchange, and published case reports describe treatment with mycophenolate, azathioprine, rituximab, infliximab, methotrexate, and tocilizumab (a monoclonal antibody targeting the interleukin-6 receptor)[3,42,43,47]. Cases of myocarditis treated with anti-thymocyte globulin have also been reported[4].

Other rheumatologic toxicities with ICIT are also described, including inflammatory arthritis, fasciitis, tenosynovitis, enthesitis, polymyalgia rheumatica, and vasculitis (including giant-cell arteritis and single-organ vasculitis)[48]. In most cases, corticosteroid therapy and nonsteroidal anti-inflammatory drug therapy are adequate to control symptoms, and ICIT can continue[3,4,15]. In refractory cases, however, additional disease-modifying anti-rheumatic drugs, including azathioprine, methotrexate, hydroxychloroquine, sulfasalazine, mycophenolate, cyclophosphamide, and tocilizumab have been used[3,4].

Renal irAEs

Reported rates of nephrotoxicity are less than 1% for anti–CTLA-4 antibodies, but acute kidney injury is reported in 2.2% of patients treated with anti–PD-1 antibodies[4]. With combination immune checkpoint blockade, renal complications are seen in 4.2% of patients[49]. Renal toxicities include glomerulonephritis, hypertension, proteinuria, and acute interstitial nephritis, with cases of lupus nephritis also reported[49].

In patients experiencing grade 1 toxicity, immune checkpoint inhibitors can be continued with careful monitoring, although holding treatment while completing a work-up for other causes (including withholding other nephrotoxic drugs, correcting volume status, and considering investigations such as urinalysis and renal ultrasonography) is also reasonable[3,15].

For grade 2 or greater toxicity, immunotherapy should be held, and corticosteroid therapy (starting with prednisone 0.5–1 mg/kg daily, with increases in doses up to 2 mg/kg daily in the absence of improvement) should be considered[3]. Nephrology consultation is advised, and renal biopsy might be required in some cases[4,15]. Other reported treatments include mycophenolate, rituximab with prednisone for cases of pauci-immune glomerulonephritis (with plasma exchange also used for a patient with positivity for anti-neutrophil cytoplasmic antibodies), and infliximab for a case of immunoglobulin A nephropathy[49,50].

SUMMARY

With the increasing use of ICIT, more patients will develop irAEs. Given the significant morbidity and potential mortality associated with those toxicities, early recognition and multidisciplinary approaches to diagnosis and management are critical. As novel immunotherapies and combination protocols continue to be developed, it is likely that additional toxicities not previously encountered will also develop over time. Ongoing research is therefore critical in reaching a better understanding of the mechanisms and management of irAEs, and the role of irAEs in predicting response to therapy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: JM has received speaking fees from EMD Serono; fees as an advisory board member for Bristol–Myers Squibb, Celgene, Novartis, and Roche; a research grant from Merck; and a travel grant from Amgen. OFK has no conflicts to disclose.

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