REVIEW ARTICLE

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Management of Immune Checkpoint Inhibitor-Related Rheumatological Toxicities

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have forged a new direction for the treatment of cancer. However, ICIs – programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors – are also known to cause immune-related adverse events (irAEs). Rheumatological adverse events are uncommon and often low grade, but flares of underlying rheumatological diseases may be triggered. Guidelines are available for the effective management of the rheumatological adverse events that more frequently arise from the use of ICIs, such as inflammatory arthritis, inflammatory myopathies, Sjogren syndrome, scleroderma, and polymyalgia rheumatica and eosinophilic fasciitis.

***Keywords*:** Immune Checkpoint Inhibitors; Immunotherapy; Immune-related Adverse Events; irAEs; Rheumatology; Inflammatory Arthritis.

INTRODUCTION

Cancer cells can evade immunosurveillance by activating immune checkpoint pathways, which suppress antitumour immune responses. The development of monoclonal antibodies that target immune checkpoints has revolutionized cancer therapy. Of these, programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors are currently approved for treating selected cancers.

However, due to their mechanism of action, immune checkpoint inhibitors (ICIs) may be associated with a range of immune-related adverse events (irAEs) [1]. For patients already with underlying autoimmune diseases such as scleroderma and systemic lupus erythematosus, which are themselves associated with an increased risk of certain cancers, irAEs may prove severe in particular. In this review, the management of ICI-related rheumatological toxicities are discussed.

MECHANISM OF ACTION

Under normal conditions, inhibitory immune checkpoint molecules negatively regulate the immune system. In particular, they regulate T-cell activity to maintain self-tolerance [2]. The suppression of immune responses with the use of these immune checkpoints in some tumour microenvironments may be responsible for compromising T-cells' antitumour activity.

ICIs inhibit these immune checkpoints, thereby restoring the normal antitumour activity of T-cells in the setting where these molecules are abnormally upregulated. Candidates for immune checkpoint blockade include CTLA-4 and PD-1, as well as one of the latter's ligands on antigen-presenting cells, PD-L1 [3].

For more than two decades, CTLA-4 has been reported to play a role in blocking CD-28-mediated costimulatory signals for T-cells in the setting of malignancy [4]. Not only is CTLA-4 blockade able to

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reject host immune responses against existing tumours, but also to potentiate immunogenicity of future tumours. Tumour cells, despite expressing immunogenic antigens on the cell surface, are sometimes able to suppress the activation of T-cells due to the presence of CTLA-4, which has been shown to bind B7 ligands at a higher affinity than CD28 [4]. Likewise, the PD-1/PD-L1 pathway normally maintains homeostasis in peripheral T-cells during inflammatory response by promoting their apoptosis [5]. It has been proven to be a possible culprit of immunosuppression in tumour microenvironments. Although monoclonal antibodies targeting PD-1 and those targeting PD-L1 block different sets of checkpoint molecule interactions, they have a common primary goal of halting PD-1/PD-L1 interaction [6].

Pembrolizumab and nivolumab, the recently approved humanized monoclonal antibodies against PD-1, have been shown to be associated with significantly longer overall survival compared to chemotherapy alone for chemotherapy-naïve metastatic NSCLC with tumour proportion score (TPS) for PD-L1 above 50%, as well as no sensitizing epidermal growth factor receptor mutation or anaplastic lymphoma kinase (ALK) gene translocation, regardless of whether combined with traditional platinum-based chemotherapy [7,8].

However, the predictive value of PD-1/PD-L1 for tumour response to these ICIs is challenged. Results from the KEYNOTE-407 study have shown that pembrolizumab combined with platinum and taxane chemotherapy yielded significantly longer overall survival, progression-free survival and objective response rate compared with chemotherapy alone for treatment-naïve metastatic squamous NSCLC [9]. As patients in the study were not selected based on and randomized for PD-L1 expression, we cannot conclude that the level of PD-L1 expression can guide treatment decisions whether to add pembrolizumab to chemotherapy. To date, multiple trials have shown the benefits of pembrolizumab without using PD-L1 expression level as an exclusion criterion for subject selection, even with PD-L1 TPS as low as 1%, supporting its use as the first-line treatment of the above selected NSCLCs disregarding PD-L1 expression level [10–12]. It is also worth mentioning that PD-L1 overexpression by NSCLC in smokers may paradoxically predict poorer efficacy of anti-PD-1 ICIs, meaning that there could also be other hidden predictors [13].

In fact, on top of quantitative PD-1/PD-L1, other tumour factors that affect antigen recognition by T-cells, including microsatellite instability and tumour mutation burden, as well as patient factors, such as cytokine, C-reactive protein levels and absolute neutrophil count, have been studied for other cancers [14]. They can potentially replace or supplement PD-1/PD-L1 expression to predict the effect of ICIs on NSCLCs.

MECHANISM AND EPIDEMIOLOGY OF AUTOIMMUNE SIDE EFFECTS

Compared to conventional cytotoxic chemotherapy, ICIs establish different toxicity profiles. They increase the total number of unique T-cell receptor sequences without a predominance of a certain clone, resulting in a non-specific increase in the diversity of T-cells in blood. Such an expansion would cause the number of auto-reactive T-cells to surge and autoimmune toxicities would ensue [15]. irAEs are associated with increased activation of the immune system which may warrant discontinuation of therapy [16]. The incidence of irAEs ranges from 15% to 90%, with severe irAEs requiring withdrawal of immunotherapy estimated to be 0.5% to 13% [17–19]. Clinical manifestations are wide ranging, most commonly dermatologic toxicities, pneumonitis, musculoskeletal disorders and endocrine disorders. Different ICIs were found to express irAEs with different severities and rates. The Common Terminology Criteria for Adverse Events system grades such adverse events based on their severity and response to treatment. In general, grade 1 refers to irAEs that do not affect quality of life. Grade-2 irAEs affect quality of life and require intervention in general. Grade-3 irAEs are similar to grade 2 except they fail to respond to simple measures. Grade-4 irAEs have severe symptoms that failed the recommended treatments for grade-2/3 irAEs [20]. irAEs associated with anti-CTLA-4 are generally more severe than those in patients treated with anti-PD-1 [21].

The irAEs in patients treated with anti-CTLA4 are usually mild to moderate and reversible with grades of 1 and 2 [16].

Apart from NSCLC, ICIs are also widely used on other malignancies, such as melanoma [22,28,31], renal cell carcinoma [23,27,29,32], Hodgkin lymphoma, ovarian cancer, etc. irAEs associated with ICIs on these malignancies were found to share similar clinical manifestations when compared to those on lung malignancy.

Advanced melanoma patients were also treated with anti-CTLA-4 or anti-PD-1 monotherapy or

Table 1. irAEs of the use of ICIs in any malignancy without pre-existing rheumatic diseases.

Immune-related events	Details
Mild skin manifestations, e.g. Rash and Pruritus [22]	Most common irAE in both combination therapy and ICI monotherapy [23] Occur 2–3 weeks after the first dose of ipilimumab [24]
Severe immune-mediated dermatitis (Toxic epidermal necrolysis, Stevens–Johnson syndrome or haemorrhagic manifestations)	Rare with a reported incidence of less than 1% [16]
Enterocolitis [23]	Typically occurring 6–7 weeks after initiation of treatment [24]
Immune-related pneumonitis [22]	Higher risk of developing immune-related pneumonitis in combination therapy than ICIs monotherapies [22,25]
Hypothyroidism [26,27]	Reported pooled incidence of 5.6% across various studies with patients receiving pembrolizumab, nivolumab and atezolizumab (total number of subjects = 3803) [26] Reported incidence among combination therapy was higher than in ICI monotherapy [27]
Hypophysitis [28,29]	Rare. More commonly observed in anti-CTLA4 monotherapy or combination therapy; rare in anti-PD-1 monotherapy [28]
Arthralgia (including those with arthritis) [22,25,31]	Reported incidence of 1–43% among 24 trials [30] Higher incidence in combination therapy than ICI monotherapy [31]
Arthritis [30,32]	Reported incidence of 1–7% among 5 trials [30] Involves 2–4 joint groups [32]
Myalgia [30,32]	Reported incidence of 2–21% among 12 trials [30] Involves 2–4 muscle groups [32]
Vasculitis [33,34]	Reported incidence of 3% in a clinical trial. Occurred in form of retinal, uterine and ovarian vasculitis [33,34]
Giant cell arteritis [35]	Reported incidence of 2% in a clinical trial [35]
Sarcoidosis [36]	Rare. Only isolated cases reported [36]
Myositis [30]	Rare. Only isolated cases of dermatomyositis and polymyositis were reported [30]

combination therapy. Common irAEs, including dermatologic toxicities, pneumonitis, arthralgia, etc., were also found in advanced melanoma patients treated with ICIs. In patients treated with anti-CTLA-4 therapy, pruritus (24.9%) and all-grade rash (20.9%) are the most frequent skin-related irAEs after dosage of ipilimumab, which share a similar pattern of skin irAE manifestations when compared to lung cancer patients treated with anti-CTLA4. Although in patients treated with anti-PD-1 therapy, all-grade eczema is found to be the most frequent skin-related irAE. Pneumonitis (all grade and grade ≥ 3) was also frequently found in anti-CTLA-4 or anti-PD-1 therapies, especially in combination therapy. The incidence of all-grade pneumonitis was 7.5% in combination therapy and 1.5% after pembrolizumab. Higher risk of developing immune-related pneumonitis in combination therapy than ICIs monotherapies was also observed in advanced melanoma patients, not limited to lung cancer [22]. Hypophysitis is more commonly observed in patients treated with anti-CTLA4 monotherapy or combination therapy, especially after the third dose of ipilimumab. However, hypophysitis is rare with anti-PD-1 monotherapy [28]. Among rheumatological irAEs, incidence of arthralgia is found to be higher in ICIs combination therapy with an incidence of 10.5% than in monotherapies, i.e. incidence of 6.1% in anti-CTLA-4 and 7.7% in anti-PD-1 group [31]. ICIs combination therapies were found to elevate the incidence of irAEs developed in advanced melanoma patients, which is also observed in lung cancer patients. Thus, extra vigilance is needed in monitoring irAEs following combination therapy, as well as skin irAEs after anti-CTLA-4 monotherapy.

In metastatic renal cell carcinoma, patients were treated either with anti-PD-1 monotherapy or with combination therapy of anti-CTLA-4 and anti-PD-1. Common cutaneous, endocrine, gastrointestinal, rheumatological irAEs were presented in both types

of therapy. Skin-related irAE of rash/pruritus was found to be most frequent in both groups of patients treated with anti-PD-1 monotherapy of nivolumab (52.2%) and combination therapy of nivolumab and ipilimumab (31.9%), sharing similar manifestation with lung cancer patients treated with ICIs. Diarrhoea/colitis was another common irAE presented in anti-PD-1 monotherapy (13%) and combination therapy (27.7%). Hypothyroidism was also frequently reported, with 8.7% in anti-PD-1 monotherapy and a much higher rate of 19.1% in combination therapy. Hypophysitis, however, was rare in both therapies [23,27]. The rate of pneumonitis was lower in renal cell carcinoma patients when compared with lung cancer patients, with only 1.5% in patients treated with anti-PD-1 [29]. Regarding rheumatological irAEs, myalgia and arthralgia were most often complained. Majority (71%) of patients complicated by myalgia and arthralgia had two to four muscle or joint groups involved.

Although the initial trials of ICI therapy excluded patients with underlying autoimmune diseases [31], recent case studies have shown that ICI therapy can flare pre-existing rheumatological disorders. According to a case series, the reported incidence was 52% of patients with rheumatological disorders and in patients with pre-existing psoriasis and immune thrombocytopenic purpura, with 38% after first dosage of anti-PD-1. The median day of onset of flare was 32–38 days after the first dosage and can range from 3 days to 7 months after onset [30,37,38]. These flares were mostly mild, mainly increased grade or recurrence of previous symptoms [30]. On the other hand, some patients with pre-existing rheumatological disorders experienced de novo irAEs [39]. Flares were found to be more frequent in patients with active symptoms and those taking immunosuppressants at the start of ICI therapy. Notably, the incidence of flares of pre-existing rheumatological disorders with ICIs was much higher than other pre-existing autoimmune disorders, since no flare was found in patients with pre-existing respiratory diseases or colitis [30]. Overall, only a few portions of patients with pre-existing autoimmune diseases present with autoimmune flares and the majority of the autoimmune conditions can be managed by corticosteroids [40]. Only a small proportion of patients required discontinuation of the ICI [30]. Therefore, close monitoring of the side effects is recommended.

ICIs are increasingly used in the treatment of different malignancies with sharing mechanisms of action. Patients of different malignancies, however, face the challenge of similar manifestations of irAEs that cause dysfunction of multiple organs, compromising their quality of life. Therefore, appropriate clinical diagnosis and management is necessary to minimize the effect and progression of irAEs.

CURRENT GUIDELINES

American Society of Clinical Oncology (ASCO) has developed treatment guidelines on ICI-related irAEs [20]. The irAEs were classified according to the severity graded in Common Terminology Criteria for Adverse Events grading system. ICIs can be continued for grade-1 irAEs except in conditions like hypophysitis, pneumonitis and sarcoidosis, while it is usually withheld for grade-2 to grade-4 irAEs until full recovery. In general, for grade-1 patients, analgesics such as NSAIDs and paracetamol can be administered; for grade-2 patients, corticosteroids like prednisone are prescribed with increasing dosage from low (0.5–1 mg/kg/day), moderate (1–2 mg/kg/day), to high (>2 mg/kg/day) as the irAEs grading increases, and they are tapered off as the irAEs subsided [41]. In case of grade-3 to grade-4 irAEs or persistent irAEs upon administration of corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate, azathioprine and mycophenolate mofetil may be given [41,42]. The treatment plan for rheumatological irAEs necessitates collaboration between oncologists and rheumatologists, and can vary from case to case [39]. Specific management guidelines for specific rheumatological diseases are discussed in the following.

Apart from conventional DMARDs as mentioned, biological DMARDs are also included in the current ASCO guidelines for the treatment of irAEs. Studies have reported that biological DMARDs including anti-Interleukin 6 receptor antibodies, e.g. tocilizumab, and anti-TNF inhibitors, e.g. infliximab, etanercept and adalimumab, were effective for the treatment of irAE [37,39,43–46]. Another review article by Jeurling and Cappelli also suggested that biologic therapies may be used in patients unresponsive to glucocorticoids and conventional DMARDs, or can be used as a steroid-sparing agent to speed up the improvement of inflammatory arthritis [43]. The use of biologic therapy for specific rheumatological manifestations of irAEs is listed in the following. Although there are case reports showing the effectiveness of biologics in treating IRAE, they are mostly limited by the small sample size. Further investigation in the use of biologic usage is required.

Inflammatory arthritis

According to the guidelines recommended by both National Comprehensive Cancer Network and ASCO, and European Society for Medical Oncology (ESMO), inflammatory arthritis is generally divided into four grades depending on the severity of pain associated with inflammation, erythema or joint swelling. For grade-1 inflammatory arthritis, ICI therapy can be continued at this stage with the prescription of analgesia with acetaminophen and/or NSAIDS (e.g. ibuprofen). The use of NSAIDs as a first-line treatment is to minimize any immunosuppression that may interfere with the anti-tumour properties of the ICIs [42]. Should NSAIDs be ineffective, prednisone 10 to 20 mg daily for 2 to 4 weeks can be administered, and increasing the dose can control most of the signs and symptoms of arthritis [42]. Intra-articular corticosteroid injection is recommended only if ≤2 joints are affected while both prednisone and NSAIDs are ineffective [20,47]. Grade-2 treatment plan should be adopted if there is no improvement of the symptoms in 2 to 4 weeks [38]. For grade-2 inflammatory arthritis, ICI therapy should be suspended while prescribing analgesia and higher doses of NSAIDs (diclofenac, naproxen or etoricoxib). Treatment dose can be slowly tapered with improvement of symptoms. However, if no improvement is shown after 4 to 6 weeks, grade-3 treatment plan should be adopted. For grade-3 to grade-4 inflammatory arthritis, ICI therapy should be suspended and oral prednisone 0.5 to 1 mg/kg should be given. In case of failure to improve after 4 weeks or deterioration after the initial treatment, DMARDs should be offered. According to case reports, methotrexate and hydroxychloroquine (HCQ) are the more common conventional DMARDs administered [42]. Various case series have shown benefits of using TNF inhibitors or IL-6 receptor antibodies in patients with irAE or inflammatory arthritis from ICI [37,42–45,48]. However, IL-6 receptor antibodies are contraindicated in patients with colitis as they potentially cause intestinal perforation. Viral hepatitis B and C tests as well as a latent or active TB test are necessary prior to DMARD prescription [20,47]. For most of the cases, as soon as the arthritis irAE is controlled, ICI therapy can be re-introduced [42]. Moreover, monitoring with routine rheumatologic examinations and inflammatory markers should be performed every 4 to 6 weeks after the initiation of treatment [20].

Early rheumatology referral is recommended for arthritis with grade 2 or above [46]. The goal is to allow early use of DMARD therapy without interrupting the ICI therapy and minimize the total dosage of systemic glucocorticoids [49].

Scleroderma

PD-1 inhibitors inducing scleroderma in patients without a previous history of autoimmune diseases have been reported. The onset is usually between 5 and 20 cycles of treatment. Common presentations include skin thickening and tightness, stiffness involving hands and feet, and Raynaud's phenomenon. The recommended first-line treatment is oral prednisone at 1 mg/kg daily [49,50]. Immediate termination of immunotherapy treatment is recommended [50], although in one case report discontinuation of immunotherapy was not required for full recovery [51]. Minimal corticosteroid should be used and the managing physician should balance the risk of exacerbating scleroderma renal crisis [49]. HCQ and topical steroids are generally not useful for scleroderma type of irAE [50]. Immunosuppressants such as mycophenolate mofetil, tacrolimus and infliximab serve as second-line treatments. They are reserved for severe or refractory cases, as well as cases where tapering of corticosteroids leads to recurrence of scleroderma [49]. A shorter immunosuppressant treatment course is recommended due to the increased risk of cancer recurrence [49]. Currently there are no clear conclusions regarding the impact of immunosuppressive therapy on the outcome of cancer treatment for patients with irAEs, yet there are retrospective series suggesting that the use of anti-TNF-alpha therapy and corticosteroids does not negatively affect survival or duration of response to cancer treatment [52].

Sicca syndrome

Sjogren's syndrome is reported in several cases usually 2 to 8 months after the administration of checkpoint inhibitors [46]. Patients typically complain of an abrupt onset of severe dry mouth accompanied by less severe symptoms of dry eyes [53]. Extraglandular symptoms including rash and sensory neuropathy are reported in some cases [54,55]. Management strategies would depend on the severity of symptoms. For mild glandular presentation, topical therapies such as artificial tears, sips of water and saliva supplements, together with sialogogues, including cevimeline and pilocarpine, may be sufficient for relieving symptoms [53]. Unlike other irAEs where immediate suspension of immunotherapy is often recommended, continuation of therapy with close monitoring could be considered in

this situation [54]. For moderate and severe glandular presentations, termination of checkpoint inhibitors is required. In addition to topical therapies and sialogogues, prednisone 20 to 40 mg daily could be administered for 2 to 3 weeks followed by a taper [54]. A higher dosage of prednisone and sialogogues could be used in refractory cases [54]. Topical treatment such as betamethasone cream should be given to patients presenting with rash [54]. As for patients diagnosed with neuro-Sjogren's syndrome, second-line treatments including cyclophosphamide or rituximab should be started as soon as possible [55]. Rituximab is generally recommended over cyclophosphamide due to the lower risk of T-cell suppression and tumour recurrence. In most cases, symptoms of Sjogren's syndrome would be improved after treatment, yet complete resolution is uncommon [54]. In the case of peripheral neuropathy, neurological deficits persist after treatment, presumably due to irreversible neuronal loss. Therefore, early diagnosis and treatment are recommended [55].

Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition that affects individuals over the age of 50 [56]. The aetiology of PMR is not well understood. One proposed mechanism is an imbalance between immunosuppressive T-regulatory lymphocytes and proinflammatory T-helper 17 cells in PMR [57]. Typical presentations of PMR include severe stiffness and pain in the shoulder muscles and pelvic girdle with normal passive range of motion of large joints [58]. A recent study demonstrated a fivefold risk of developing PMR as an irAE in patients undertaking ICI therapy, though the manifestations of PMR as an irAE often contain atypical features. This led to the discussion whether the irAEs are new entities or are identical to the idiopathic form of PMR [48]. The severity of PMR is classified into four grades. Grade 1 includes patients with mild stiffness and pain. In this case, ICI therapy could be continued while analgesia with acetaminophen and/or NSAIDs would be initiated if there are no contraindications. Grade 2 includes patients with moderate stiffness and pain together with limiting age-appropriate instrumental activity of daily living (ADL). It is recommended that ICI should be withheld and prednisolone <10 mg could be prescribed. ICI can be resumed upon symptom control [20]. In some cases where response is limited with low dose, prednisone 20 mg/d or equivalent could be initiated, and tapered if symptoms improve after 3 to 4 weeks. Referral to rheumatology should be considered. For grade-3 to grade-4 patients with severe stiffness and pain with limiting self-care ADL, ICI should be withheld and resumed upon consultation with a rheumatologist. Prednisone 20 mg/d or equivalent should be initiated. If there is no improvement, a corticosteroid-sparing agent like methotrexate or tocilizumab may be considered [20,41,42]. The success of using tocilizumab suggests a role of IL-6 and Th-17 cells in the development of irAEs for ICI therapy [48].

Inflammatory myopathies

Inflammatory myopathies are a group of immune-mediated disorders of muscle injury. These include dermatomyositis, overlap syndromes, inclusion body myositis, immune-mediated necrotizing myopathy and polymyositis [59]. Proximal skeletal muscle weakness is the typical clinical manifestation. Diagnosis depends on complete rheumatologic and neurologic history and examination with blood tests showing elevation of muscle enzymes. Management of this group of irAE would depend on the severity. For grade-1 patients with mild muscle weakness with or without pain, ICI therapy could be continued while corticosteroids, analgesia with acetaminophen or NSAIDs would be offered if not contraindicated. Multiple case reviews have shown good response with an initial dose of 70 mg prednisolone or equivalent. However, during tapering of glucocorticoids, the disease activity of myositis often increases, requiring referral to a rheumatologist for other treatments [42]. For grade-2 patients with moderate muscle weakness with or without pain and limiting age-appropriate instrumental ADL, ICI should be held temporarily while corticosteroids and NSAIDs could be administered. Referral to rheumatologist or neurologist and permanent discontinuation of ICI therapy are also recommended. For grade-3 patients with severe muscle weakness with or without pain and limiting self-care ADL, ICI therapy should be held while prednisone 1 mg/kg or equivalent would be initiated. Intravenous methylprednisolone 1 to 2 mg/kg or higher bolus dose would be required if patients are severely compromised. If the symptoms do not improve or worsen after 4 to 6 weeks, hospitalization would be recommended with prompt referral to rheumatologist or neurologist to consider other treatment options including plasmapheresis and intravenous immunoglobulin (IVIG) therapy, often combined with other immunosuppressant therapy, such as methotrexate, azathioprine, mycophenolate mofetil

or infliximab [20,41,42]. According to case reviews, the response could range from complete remission to lethal outcomes, but this often depends on the initial severity of the myositis [42].

Eosinophilic fasciitis

Eosinophilic fasciitis (EF) is a rare irAE. It involves inflammation, thickening and fibrosis of the fascia [60, 61]. Clinically, it is characterized by oedema, erythema and induration of the skin in the extremities. It could also present as peripheral eosinophilia [60]. Although it mimics scleroderma in some aspects like skin tightening, patients with EF do not present with other typical scleroderma signs including Raynaud's phenomenon, sclerodactyly and telangiectasias.

Pinal-Fernandez proposed the classification criteria for EF in 2014. After ruling out systemic sclerosis, EF could be diagnosed when two major criteria are met: (1) induration or swelling of the skin and subcutaneous tissues and (2) thickening of the fascia with lymphocyte and macrophage accumulation with or without infiltration of eosinophils in skin biopsy [62]. If only one of them is satisfied, EF could be established with the co-existence of any two of the five minor criteria: (1) eosinophilia, (2) hypergammaglobulinemia, (3) groove sign, (4) hyperintense fascia on T2-weighted image in MRI and (5) muscle weakness [62].

The treatment of EF-irAE is currently not well documented due to limited available literature. The recommended first-line therapy is corticosteroids. It was found that more than 70% of the EF patients have partial to complete response to oral prednisone alone [63]. Methotrexate could be used if there is inadequate response to corticosteroids. In a study consisting of 63 patients with EF, 64% of the subjects achieved complete response to the combination of prednisone and methotrexate [64]. In another retrospective study with 32 EF patients, complete remission was achieved in 69% of the patients with the use of prednisone alone or prednisone and methotrexate [65].

Besides, HCQ was also shown to be beneficial in treating EF. In a retrospective review with 16 patients, complete response was achieved in 25% of the patients in HCQ monotherapy or HCQ with corticosteroid [63]. However, HCQ was not shown to be superior to corticosteroids alone. D-penicillamine is another drug found to be beneficial for EF. In a prospective non-randomized study with 16 patients with EF, patients treated with D-penicillamine and corticosteroid were found to have significantly more clinical improvement compared with those being treated with corticosteroids alone [66]. However, D-penicillamine may cause a lot of severe side effects including bullous pemphigoid, proteinuria, leukopenia and myasthenia gravis [67]. All of these limit the use of D-penicillamine in treating EF. Furthermore, immunomodulators including IVIG therapy, mycophenolate mofetil, azathioprine, cyclosporine, sirolimus, infliximab, rituximab and tocilizumab have also been utilized to treat EF [60]. Nevertheless, their true efficacies are yet to be determined.

Systemic vasculitis

Despite being rare, various forms of vasculitides have been observed as irAEs for ICI therapy, including large-vessel vasculitis and systemic medium- and small-vessel vasculitides [68]. They generally occur later than other rheumatological irAEs, at a median of 3 months after initiating ICI therapy [69]. According to case reviews, most patients developed either large-vessel vasculitis or vasculitis of the central nervous system [70]. The pathophysiology of giant cell arteritis (GCA) is poorly understood, but it is involved with T-cell and macrophage infiltration of the vessel wall and cytokine production [68]. A recent study has found that dendritic cells in the vessel wall, which express PD-L1 and PD-L2 on their surfaces, help protect the wall against immune cell infiltration, suggesting the role of the PD-1 axis in the pathophysiology of GCA [71]. According to a large retrospective study of the WHO Global Database for Case Safety, ICI therapy was associated with a greater risk of GCA [68]. Genome-wide association studies have also found that polymorphisms in the PDCD1 gene encoding for PD-1 and the CTLA-4 gene encoding for CTLA-4 have higher incidences of medium- to small-vessel vasculitis such as Kawasaki disease, Behcet's disease and granulomatosis with polyangiitis [70].

The management of vasculitis as an irAE was not included in the ASCO guidelines owing to its rarity, and there are therefore no definitions for grading the vasculitis from grade 1 to grade 4 unlike other rheumatological irAEs [39, 69]. The *Journal of Clinical Oncology* has stated that the management and treatment principles of such irAEs are similar to the other irAEs [20]. The treatment largely depends on the underlying malignancy and the manifestation of the vasculitis [69]. According to multiple case reviews, discontinuation of the ICI and systemic glucocorticoids such as prednisone at an initial dose of

60 mg produced a good response, especially in the lesions in the skin and the gastrointestinal tract [42,70,72]. If there is no improvement of symptoms within 48 to 72 hours of initiating high-dose steroids, infliximab can be offered. Some other case reports, especially those for small-vessel vasculitis, have also reported efficacy of using hydroxychloroquine, botulinum toxin, rituximab or cyclophosphamide [73]. If the initial symptoms of vasculitis are severe, permanent discontinuation of the ICI is needed [69].

CONCLUSION

The use of ICIs is one of the first breakthroughs in the treatment of malignancy, regardless of histological subtype. However, irAEs induced by ICIs may cause new-onset or exacerbate underlying autoimmune diseases. Despite the infrequent occurrence of rheumatological adverse effects, treatments requiring immunosuppressants and steroids may have long-standing consequences. ICIs continue to be strongly recommended for the treatment of malignancies with high TPS, as the benefits to overall survival do outweigh possible adverse effects, which are uncommon and mostly of minimal morbidity.

Further investigation into the molecular relationship between the immune response and the mechanism of action of such ICIs should be done to refine the current regimen and establish a clearer safety profile for the drug. Communication between the rheumatologist and the oncologist would be essential to achieve the best treatment strategy.

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