RHEUMATOLOGY

Rheumatology 2019;58:vii40–vii48
doi:10.1093/rheumatology/kez297

Frequency and distribution of various rheumatic disorders associated with checkpoint inhibitor therapy

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Abstract

Immune checkpoint inhibitors have advanced the treatment paradigm of various cancers, achieving remarkable survival benefits. However, a myriad of immune-related adverse events (irAE) has been recognized in almost every organ system, presumably because of persistent immune system activation. Rheumatic symptoms such as arthralgia or myalgia are very common. More specific irAE are increasingly being reported. The most frequent ones are inflammatory arthritis, polymyalgia-like syndromes, myositis and sicca manifestations. These rheumatic irAE can develop in ~5–10% of patients treated with immune checkpoint inhibitors, although true incidence rates cannot be estimated given the lack of prospective cohort studies, and likely underreporting of rheumatic irAE in oncology trials. In this review, we will provide a summary of the epidemiologic data reported for these rheumatic irAE, until more robust prospective longitudinal studies become available to further define the true incidence rate of rheumatic irAE in patients receiving these novel cancer therapies.

Key words: rheumatic syndromes, immune-related adverse events, immune checkpoint inhibitors, cancer

SUPPLEMENT

Rheumatology key messages

- Immune checkpoint inhibitor therapy can induce a broad spectrum of rheumatic immune-related adverse events.
- Rheumatic immune-related adverse events are more frequent in patients receiving anti-programmed cell death-1/programmed cell death-ligand 1 therapy or combination immune checkpoint inhibitors.
- Rheumatic immune-related adverse events such as myositis and vasculitis can be serious and cause death.

Introduction

Rheumatic immune-related adverse events (irAE) are increasingly being reported in patients with cancer receiving therapy with immune checkpoint inhibitors (ICI). While the incidence of many non-rheumatic irAE is well known, the true incidence of rheumatic irAE is not as precise, partly because rheumatic manifestations may be underrecognized by oncologists, are presumably underreported in ICI clinical trials and may be dismissed when they do not pose life-threatening complications. Oncology trials use the Common Terminology Criteria for Adverse Events to categorize adverse events, which are not suitable to characterize the broad spectrum of rheumatic manifestations that may occur in patients receiving ICI [1]. For instance, different codes can be used for joint manifestations including pain in different joints, joint effusion, arthritis or restriction in the range of motion. Similarly, myalgia, muscle weakness or myositis can be used for coding myopathy. Rheumatic adverse events are often coded as grade 2 in the Common Terminology Criteria for Adverse Events, if they are not perceived to be urgent or life-threatening, and many trials only report grade 3–5 adverse events.

Lack of awareness about rheumatic irAE represents a major challenge in the recognition and management of these toxicities. In an online survey performed in the USA in 2016 and in France in 2018, >70% of the rheumatologists were unfamiliar with ICI-induced irAE, and >90% reported not being confident in managing these patients [2]. Similar findings were reported in a 2017 survey of Portuguese rheumatologists and oncologists [3].

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Submitted 9 April 2019; accepted 17 June 2019

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The most commonly reported rheumatic irAE include arthralgia and arthritis, polymyalgia-like syndromes, myositis and sicca syndromes. The largest cohort of patients with rheumatic irAE is a single-centre, retrospective study that reported 43 cases among 1293 patients treated with ICI, with a prevalence of 3.3% [4]. A single-centre French study reported that of 524 patients receiving ICI, 6.6% were referred to rheumatology [5]. The following sections provide a summary of the epidemiologic data reported for these irAE, as well as for others less frequently reported, recognizing that well-conducted, prospective studies adequately ascertaining rheumatic syndromes are not available at this time. Incidence rates cannot be adequately established as for most studies length of therapy in the sample treated is not provided.

Methods

Identification of studies

We conducted a search in Medline from inception to March 2019. Search terms included ICI terms ('anti-CTLA-4', 'anti-PD-1', 'anti-PD-L1', 'ipilimumab', 'nivolumab', 'pembrolizumab', 'atezolizumab', 'durvalumab', 'avelumab'), and various rheumatic and autoimmune terms ('arthralgia', 'arthritis', 'arthropathy', 'myositis', 'myalgia', 'myasthenia', 'osteoporosis', 'osteopenia', 'synovitis', 'tenosynovitis', 'sicca', 'Sjogren', 'systemic lupus erythematosus', 'subacute cutaneous lupus', 'antiphospholipid syndrome', 'antiphospholipid antibodies', 'systemic sclerosis', 'scleroderma', 'sarcoidosis', 'hemolytic uraemic syndrome', 'thrombotic thrombocytopenic purpura', 'hemophagocytic lymphohistyocytosis', 'vasculitis', 'necrotizing vasculitis', 'cutaneous vasculitis', 'Henoch schonlein purpura', 'granulomatosis with polyangiitis', 'microscopic polyangiitis', 'eosinophilic granulomatosis with polyangiitis', 'ANCA vasculitis', 'rheumatic', 'musculoskeletal' and 'immune-related adverse events'). Additionally, references of the included articles were searched manually to identify relevant studies. In the following sections, we summarize data on various rheumatic irAE obtained from systematic reviews, observational studies with pooled results, registry data, case reports and case series with individual description of cases. When multiple publications of the same study were identified, data were obtained from the most recent publication. Table 1 summarizes the demographics and baseline characteristics of case reports and series presenting with various rheumatic irAE following ICI therapy.

Common rheumatic immune-related adverse events

Arthralgia and arthritis

Two systematic reviews on musculoskeletal and rheumatic irAE included ICI clinical trials in different cancer types, and reported arthralgia as the most common rheumatic irAE with an estimated prevalence ranging from 1 to 43%, with inflammatory arthritis occurring less frequently, in 1–7% of patients [6, 7]. Another systematic review identified the rates of organ-specific irAE induced by anti-programmed cell death-1 (anti-PD-1)/anti-programmed cell death-ligand 1 (PD-L1) agents, but owing to the inconsistent reporting of musculoskeletal irAE, they were unable to perform meta-analysis for this subgroup of events [8].

We recently reviewed the published literature on inflammatory arthritis induced by ICI from May 2017 to November 2018 and summarized all case reports and series [9]. A few observational studies have provided data on the prevalence of arthritis. The French registry 'Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie (REISAMIC)' includes patients with grade $\geqslant$2 irAE; of the 908 patients who received anti-PD-1/PD-L1 agents between 2012 and 2016 [10], 7 (0.7%) were reported to have developed seronegative arthritis, 2 (0.2%) RA and 2 (0.2%) PsA. In patients treated with anti-PD-1/PD-L1 in combination with anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) agents, the prevalence increased to 2.5%. In another retrospective single-centre study of 400 patients with melanoma who had received ICI, arthritis occurred in 12 patients (3%) [11]. In the French study referenced above reporting musculoskeletal irAE in 524 patients receiving ICI, the most common presentation was arthralgia, with 20 (3.8%) patients developing inflammatory arthritis [5]. Another retrospective single-centre study of 195 of patients with cutaneous malignancy who had received anti-PD-1 (single agent or in combination with ipilimumab) reported arthralgia in 26 (13.3%) patients, with *de novo* inflammatory arthritis in 10 patients (5.1%). In addition, active synovitis in joints that were previously damaged by OA occurred in another five patients, suggesting that inflammatory events can occur in patients with degenerative joint disease who receive ICI [12].

Our review of the literature also identified a total of 90 patients with *de novo* inflammatory arthritis induced by ICI therapy that were published recently in case reports and small series, which aids in the categorization of the different types of arthritis irAE [9] (Table 1). Inflammatory polyarthritis was the most frequently reported presentation. The median (range) age of these patients was 64.5 (41–81) years, 57% were male, 48% had melanoma and most (98%) received anti-PD-1/PD-L1 agents, including nine patients who received combination ICI. Median time to onset of symptoms after initiation of treatment was 3 (0.1–24) months [10, 11, 13–25]. RA as such was reported in 10 patients [10, 26, 27]. Their median age was 61.5 (54–80) years, 50% were female, 40% had lung cancer and all of them had received anti-PD-1 agents. Median time to onset of symptoms after initiation of treatment was 1 (0.1–5) months. PsA was reported in six patients [10, 28–30]. Their median age was 64.5 (53–72) years, 50% were male, 67% had lung cancer and all of them had received anti-PD-1 therapy. Median time to onset of symptoms after initiation of treatment was 1.5 (0.5–22) months. In addition, other types of inflammatory arthritis including undifferentiated oligoarthritis [11, 13–16, 18, 20]

Table 1 Demographics and baseline characteristics of case reports/series presenting with rheumatic irAE

Type of rheumatic irAE[a]	No. of cases	Age, years [median (range)]	Gender (%)	Type of cancer (%)	Type of ICI (%)	Time to symptoms onset after ICI initiation, months [median (range)]
Inflammatory polyarthritis	40	64.5 (41–81)	Male (57)	Melanoma (48)	Anti-PD-1/PD-L1 agents, ICI combination (98)[b]	3 (0.1–24)
RA	10	61.5 (54–80)	Male (50)	Lung cancer (40)	Anti-PD-1 agents (100)	1 (0.1–5)
PsA	6	64.5 (53–72)	Male (50)	Lung cancer (67)	Anti-PD-1 agents (100)	1.5 (0.5–22)
Polymyalgia rheumatica	24	71.5 (50–88)	Male (64)	Melanoma (50)	Anti-PD-1/PD-L1 agents, ICI combination (92)	3.3 (0.3–16)
Myositis	48	68 (36–89)	Male (55)	Melanoma (71)	Anti-PD-1/PD-L1 agents, ICI combination (90)	1 (0.4–3)
Sicca syndrome	17	63 (36–81)	Male (53)	Melanoma (71)	Anti-PD-1/PD-L1 agents, ICI combination (88)	3.8 (0.5–10)
Sarcoidosis	53	57 (26–79)	Male (47)	Melanoma (74)	Anti-PD-1/PD-L1 agents, ICI combination (67)	4.3 (0.3–45)
Vasculitis[c]	20	53 (31–78)	Male (53)	Melanoma (75)	Anti-PD-1 agents, ICI combination (60)	3.5 (0.25–18)

[a]A few other cases with rheumatic irAE were reported including reactive arthritis, undifferentiated oligoarthritis, monoarthritis, undefined cases with inflammatory arthritis, remitting seronegative symmetrical synovitis with pitting oedema, inflammatory tenosynovitis, Jaccoud's arthropathy, dermatomyositis, antisynthesase syndrome, lupus erythematosus, APS, scleroderma-like syndromes, hemophagocytic lymphohistiocytosis and bone abnormalities. [b]Few patients were receiving anti-PD-1 or anti-PD-L1 in combination with ipilimumab or tremelimumab. [c]Reported vasculitis types include GCA, aortitis, primary angiitits of the CNS, isolated vasculitic neuropathy, uterine lymphocytic vasculitis, temporal arteritis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and retinal, digital, cryoglobulinaemic, granulomatous, autoimmune, necrotizing, cutaneous small vessels and acral vasculitis. irAE: immune-related adverse events; ICI: immune checkpoint inhibitor; anti-PD-1/PD-L1: anti-programmed cell death-1/anti-programmed cell death-ligand 1.

and monoarthritis [11, 14], and other undefined cases with inflammatory arthritis were also reported [31]. An earlier publication described a series of nine patients with inflammatory arthritis induced by ICI, with a few of them presenting also with urethritis and conjunctivitis, consistent with the diagnosis of reactive arthritis [32].

Three patients developed remitting seronegative symmetrical synovitis with pitting oedema after receiving nivolumab for melanoma [33–35]. All were male, and their age ranged from 70 to 80 years. Median time to onset of symptoms after initiation of treatment was 3 (1–4) months.

Other unusual presentations have also been described in case reports and series including inflammatory tenosynovitis involving hands and/or shoulders, enthesitis and swan neck deformities consistent with Jaccoud's arthropathy [15, 18, 36].

Overall, different patterns of inflammatory arthritis have been reported in the literature following ICI therapy, predominantly anti-PD-1 agents or combination ICI. While in many cases arthritis occurred within the first few months of ICI initiation, several patients developed late-onset inflammatory arthritis, which persisted even after ICI discontinuation. About half of the patients who developed inflammatory arthritis also had non-rheumatic irAE.

Polymyalgia rheumatica

Studies using Vigibase, from the World Health Organization Individual Case Safety Reports (ICSRs) pharmacovigilance database, which combines reports from 130 countries around the world, reported a higher frequency of polymyalgia rheumatica in patients receiving ICI, compared with reports in the full database [37]. Overall, polymyalgia rheumatica was reported in 16 patients; their median age was 75.5 (63–88) years, 67% were males and 69% had melanoma. There were more reports of polymyalgia in patients receiving anti-PD-1/PD-L1 (single agent or combination ICI) compared with those receiving anti-CTLA-4 agents (15 *vs* 1), presenting after 2.6 (0.6–5.6) months of ICI initiation. Vision was impaired in one patient (6%), associated rheumatic irAE occurred in four (25%) and non-rheumatic irAE in six (38%). In the REISAMIC registry, only two patients with polymyalgia rheumatica were reported among 908 patients who had received anti-PD-1/PD-L1 agents, with an estimated prevalence of 0.2% [10]. In a single-centre prospective cohort study, 11 (2.1%) out of 524 patients who had received ICI therapy developed polymyalgia rheumatica symptoms, predominantly associated with anti-PD-1/PD-L1 therapy [5]. All patients except one fulfilled the 2012 EULAR/ACR for diagnosis of polymyalgia rheumatica.

A total of 24 patients with *de novo* polymyalgia rheumatica induced by ICI therapy have been published in case reports and small series [4, 10, 16, 20, 26, 38–45] (Table 1). The median age of these patients was 71.5 (50–88) years, 64% were male, 50% had melanoma and 92% received anti-PD-1/PD-L1 agents, including three patients who received combination ICI. Median time to onset of symptoms after initiation of treatment was 3.3 (0.3–16) months. Two patients had associated sicca symptoms and six others had non-rheumatic irAE.

Myositis

Three systematic reviews have previously reported the occurrence of myalgia as the second most common rheumatic irAE in ICI clinical trials with an estimated prevalence ranging from 2 to 21%, but no clear specification as to the likely diagnosis associated with this symptom. Myositis was less frequently reported, occurring in 0.4–6% of the patients [7, 8, 46].

In the ICSRs pharmacovigilance database, ICI therapy was associated with 180 reports of myositis through March 2018; most cases developed following the administration of anti-PD-1 agents (single agent or combination ICI) [47]. The median age of these patients was 71 (62.3–76) years, 62% were male, 31% each with melanoma or lung cancer, and 98% received anti-PD-1/PD-L1 agents, including 27 patients (15%) who received combination ICI. Median time to onset of symptoms after initiation of treatment was 26 (18–39) days. Of the 180 reported cases with myositis, 29 patients (16%) had myocarditis and 28 (15.6%) had myasthenia gravis. Death occurred in 36 patients (21.2%). In the US Food and Drug Administration Adverse Events Reporting System, ICI therapy was associated with 160 reports of inflammatory myopathy between 2004 and 2016, including polymyositis, dermatomyositis and necrotizing myositis; there were more reports in patients receiving anti-PD-1 than in those receiving anti-CTLA-4 therapy (118 *vs* 42, respectively) [48].

The REISAMIC registry reported three patients with myositis among 908 patients who had received anti-PD-1/PD-L1 agents with an estimated prevalence of 0.3% [10]. In a retrospective study of 654 patients who had received anti-PD-1 at the Mayo Clinic, 5 (0.7%) developed myopathy, as defined by the authors, confirmed by biopsy after initiation of pembrolizumab, including 2 each with necrotizing myopathy or non-specific myopathy, and 1 with dermatomyositis [49]. More recently, another retrospective study at the Mayo Clinic that focused on rheumatic irAE and included a total of 1293 patients who had received ICI identified 10 patients with myopathy with an estimated prevalence of 0.8% [4]. Nine patients (90%) had received anti-PD-1 therapy; four (40%) had associated myocarditis. Myositis-related death occurred in two patients. Another retrospective multicentre study in Europe identified a series of 10 patients with myositis; their median age was 73 (56–87) years, 70% were male and 50% had melanoma, and all of them occurred after initiation of anti-PD-1, including two patients who received combination ICI [50]. Four of these patients (40%) had confirmed or possible myocarditis, four had other non-rheumatic irAE and none died because of myositis. More recently, another retrospective multicentre study reported 38 patients with neuromuscular toxicity induced by ICI therapy, including 19 patients with myositis, all after initiation of anti-PD-1 agents, including 5 who received combination ICI [51]. A third of the patients developed myocarditis. Two patients died, with the cause of death being attributed to the myositis in two patients (5%).

We have identified in case reports and series a total of 48 patients with ICI-induced myositis [14, 16, 38, 43, 52–64] (Table 1). The median age of these patients was 68 (36–89) years, 55% were male, 71% had melanoma and 90% received anti-PD-1/PD-L1 agents, including 13 patients (32%) who received combination ICI. Median time to onset of symptoms after initiation of treatment was 1 (0.4–3) month. Thirteen patients (27%) had myasthenia gravis and nine (19%) had myocarditis.

Three patients with *de novo* dermatomyositis have been reported, two after initiation of ipilimumab [51, 65] and one after receiving nivolumab [66]. Another patient developed antisynthesase syndrome after therapy with nivolumab [43].

Sicca syndrome

Two systematic reviews of ICI trials have reported sicca symptoms as a mild irAE with an estimated prevalence of 1.2–24.2% [7, 46], all cases following the administration of anti-PD-1 agents.

The REISAMIC registry reported 4 patients with Sjögren syndrome among 908 patients who had received anti-PD-1/PD-L1 therapies, with an estimated prevalence of 0.3% that increased to 2.5% among patients treated with combination ICI [10]. The median age of these patients was 59 (56–76) years, 75% were female and they had different malignancies (melanoma, renal cell and genitourinary cancer). All received anti-PD-1/PD-L1 agents, including one who received combination ICI. The median time to onset of symptoms after initiation of treatment was 2.3 (1–2.6) months. All patients fulfilled the criteria of the American-European Consensus group 2002 and ACR/EULAR criteria 2017 for true Sjögren syndrome; one had associated cryoglobulinaemic vasculitis.

An additional 17 patients with *de novo* sicca symptoms have been published in small series [4, 14, 16, 32, 38, 67] (Table 1). The median age of these patients was 63 (36–81) years, 53% were male, 71% had melanoma and 88% received anti-PD-1/PD-L1 (single agent or combination ICI). Median time to onset of symptoms after initiation of treatment was 3.8 (0.5–10) months. All patients had salivary gland hypofunction, five had dry mouth without keratoconjunctivitis and only one reported having bilateral parotid gland enlargement with US features suggestive of Sjögren syndrome. Five patients had other rheumatic irAE including arthritis and polymyalgia rheumatic; seven also had non-rheumatic irAE.

Other rheumatic immune-related adverse events

Sarcoidosis

A publication using data from the BIOGEAS registry, which comprises reports of patients who develop autoimmune manifestations after receiving a biologic therapy, included 913 patients who experienced irAE after initiation of ICI therapy. Of these, there were 20 patient reports of sarcoidosis (13 had received ipilimumab and 7 anti-PD-1 agents) [68]. Most had melanoma. The data provided were

insufficient to determine the degree or the organs involved. A single-centre retrospective study of 147 patients with melanoma who received ipilimumab reported that 8 (5%) developed sarcoid-like lymphadenopathy after a median of 3.2 (0.2–9.1) months of ipilimumab treatment [69]. All eight patients had mediastinal and hilar lymphadenopathy, and one had intra-abdominal lymphadenopathy. In the REISAMIC registry, only two patients with sarcoidosis were reported, with an estimated prevalence of 0.2% [10].

A total of 53 patients with sarcoid-like granulomatous lesions induced by ICI therapy have been published in case reports and small series [10, 11, 70–91] (Table 1). The median age of these patients was 57 (26–79) years, 53% were female, 74% had melanoma and 67% received anti-PD-1/PD-L1 agents, including nine patients who received combination ICI. Median time to onset of symptoms after initiation of treatment was 4.3 (0.3–45) months. Pulmonary and/or skin manifestations were most common. Most patients did not develop other irAE.

Vasculitis

A recent systematic review identified 20 cases with *de novo* onset vasculitis induced by ICI therapy, fulfilling the 2012 revised International Chapel Hill Consensus Conference nomenclature for vasculitis [92] (Table 1). The median age of these patients was 53 (31–78) years, 53% were males, 75% had melanoma and 60% received anti-PD-1, including one who received combination ICI. Median time to onset of vasculitis symptoms after ICI initiation was 3.5 (0.25–18) months. The predominant type of vasculitis was large vessels (GCA and aortitis) or nervous system vasculitis (primary angiitis of the central nervous system and isolated vasculitic neuropathy). Other reported vasculitis types included uterine lymphocytic vasculitis, granulomatosis with polyangiitis, and retinal, digital, cryoglobulinaemic, granulomatous and autoimmune vasculitis.

In the ICSRs pharmacovigilance database, ICI therapy was associated with a significantly higher reporting of vasculitis and temporal arteritis compared with the full database [37]. Overall, 82 vasculitis adverse events were reported in patients who had received ICI, more frequently anti-PD-1/PD-L1 (single agent or combination ICI) therapy compared with those receiving anti-CTLA-4 agents (64 *vs* 18). Temporal arteritis was reported in 18 patients; their median age at symptom onset was 72.9 (60–83) years, 53% were males and 77% had melanoma. There were more reports of patients with temporal arteritis who received anti-CTLA-4 than who received anti-PD-1/PD-L1 therapy (10 *vs* 8). Median time to onset of arteritis symptoms after ICI initiation was 0.7 (0.7–4.4) months. Vision was impaired in five patients (28%), and associated irAE occurred in 11 patients (61%). Of the 82 patients with vasculitis, death occurred in five patients (6%), but none of them had temporal arteritis. In the BIOGEAS registry, five patients had vasculitis reported in relation to ICI therapy (three cases induced by ipilimumab and two others induced by anti-PD-1 agents); no sufficient information was provided on the patients' demographics and type of vasculitis [68].

A few other patients with *de novo* vasculitis induced by ICI therapy have been published in case reports and series. Five patients with necrotizing vasculitis were reported in two small series, primarily after receiving anti-PD-1 agents [4, 93]. Only two of them had positive perinuclear ANCA. Two melanoma patients developed GCA within 4.4 (3.3–5.5) months after initiation of ipilimumab; one of them had active arteritis on temporal biopsy [94]. Another three reports included patients with eosinophilic granulomatosis with polyangiitis, cutaneous small vessels vasculitis and acral vasculitis [95–97].

Lupus erythematosus

In the REISAMIC registry, 5 of 1044 patients who had received anti-PD-1/PD-L1 therapy developed *de novo* lupus with an estimated prevalence of 0.48% [98]. Median age of these patients was 63 (48–80) years, 60% were female, 40% had melanoma and all of them received anti-PD-1/PD-L1 monotherapy. Median time to onset of symptoms after initiation of ICI was 2.5 (1–5.5) months. Four patients had scLE, including one who also had arthralgia and positive serum antibodies fulfilling the SLICC criteria for systemic lupus. Another patient had chilblain lupus. Of the five patients, three also had non-rheumatic irAE. The BIOGEAS registry reported only one case of SLE in a patient receiving ipilimumab [68]. The BIOGEAS registry did not report any case of SLE in relation to anti-PD-1 therapy.

Four additional patients with *de novo* lupus have been published in case reports [99–101]. All had scLE developing within 0.5–8.5 months after starting anti-PD-1 therapy. Another report described a 64-year-old male who developed LN with positive anti-dsDNA after receiving two doses of ipilimumab [102].

APS

Only one patient with APS induced by ICI therapy has been reported [103]. A 62-year-old male with metastatic melanoma presented with violaceous patches over the palms and planter surfaces of feet with gangrenous tips of fingers and toes after receiving a combination of ipilimumab and nivolumab, thrombotic occlusion of several arterioles in the dermis and elevated anti-β-2 glycoprotein 1 antibodies (immunoglobulin M isotype). Another patient had a positive lupus anticoagulant test after his third dose of nivolumab, but without clinical manifestations [104].

Scleroderma-like syndromes

Four patients have developed diffuse scleroderma-like syndromes after ICI therapy [4, 105]. All were males who had received anti-PD-1 therapy; median time to onset of skin manifestations after starting ICI was 8 (3.8–9.8) months.

Two patients with melanoma developed eosinophilic fasciitis, one of them a month after completing 18 months of pembrolizumab [11, 106]. One patient developed lymphocytic fasciitis after 2 years of nivolumab therapy

[107]; another one presented with myofasciitis and tenosynovitis 10 months after receiving nivolumab [108].

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis after ICI therapy was reported in the ICSRs pharmacovigilance database in 26 patients who received anti-CTLA-4 or anti-PD-1/PD-L1 agents [109].

Three cases reports of hemophagocytic lymphohistiocytosis after ICI therapy have been published. Two had received a single dose of ICI combination therapy; one of them also had myositis, myasthenia gravis and neuropathy [58, 110]. The third patient developed hemophagocytic lymphohistiocytosis after six doses of pembrolizumab [111].

Bone abnormalities

Compression fractures and resorptive bone lesions have recently been reported as skeletal irAE in a small series of six patients who had received ICI [21]. The median age of these patients was 59 (51–75) years, 83% were male and 67% had melanoma. Four received anti-PD-1 monotherapy and the other two combination ICI. Three patients had vertebral compression fractures within 10–15 months after treatment initiation, two with multiple vertebral fractures, and one had additional pelvic and rib fractures. None of these patients had other identifiable risk factors for osteoporosis, and none had a T-score >−2.5 on dual-energy X-ray absorptiometry testing. Three other patients had resorptive bone lesions of shoulder, clavicle or wrist; all of them had arthritis irAE in other joints, and one patient had also non-rheumatic irAE. Median time to onset of symptoms after initiation of treatment was 8 (1–18) months.

Osteonecrosis of the jaw was reported in two patients after ICI therapy: ipilimumab and nivolumab, respectively [112].

Summary

The hallmark of ICI therapy is the durable clinical response owing to the persistent activation of immune system; nevertheless, such a response could result in a broad spectrum of irAE in various organs. Inflammatory arthritis, polymyalgia rheumatica, myositis and sicca syndrome are the most frequently encountered rheumatic irAE, occurring in up to 10% of patients receiving ICI therapy, yet their true incidence rates are not precisely known. Other less frequently reported rheumatic irAE include sarcoidosis, vasculitis, lupus erythematosus, APS, scleroderma-like syndromes, hemophagocytic lymphohistocytosis and bone abnormalities. The majority of the cases of rheumatic irAE are reported following anti-PD-1/PD-L1 monotherapy or combination ICI therapy, with a variable time to onset, sometimes months after ICI initiation. Inflammatory arthritis may persist in some patients despite ICI discontinuation. Rheumatic irAE can be clinically challenging and sometimes fatal, primarily in patients with ICI-induced myositis and vasculitis. Well-conducted prospective cohort studies of cancer patients receiving ICI in real-world settings are necessary to establish the true incidence of rheumatic irAE and their clinical consequences.

Funding: This paper was published as part of a supplement funded by an educational grant from BMS.

Disclosure statement: M.E.S.-A. has received consultant fees from Pfizer, AbbVie and Eli Lilly outside the submitted work. The other author declares no conflicts of interest.

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