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REVIEW ARTICLE

Musculoskeletal and Rheumatic Diseases Induced by Immune Checkpoint Inhibitors: A Review of the Literature

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ARTICLE HISTORY

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Abstract: ***Background*:** Immune checkpoint inhibitors are a new promising class of antitumor drugs that have been associated with a number of immune-related Adverse Events (AEs), including musculoskeletal and rheumatic disease.

***Methods*:** We searched Medline reviewing reports of musculoskeletal and rheumatic AEs induced by immune checkpoint inhibitors.

***Results*:** Several musculoskeletal and rheumatic AEs associated with immune checkpoint inhibitors treatment are reported in the literature. In particular, arthralgia and myalgia were the most common reported AEs, whereas the prevalence of arthritis, myositis and vasculitis is less characterized and mainly reported in case series and case reports. Other occasionally described AEs are sicca syndrome, polymyalgia rheumatica, systemic lupus erythematosus and sarcoidosis.

***Conclusion*:** Newly induced musculoskeletal and rheumatic diseases are a frequent adverse event associated with immune checkpoint inhibitors treatment.

Keywords: Immune checkpoint inhibitors, anti-PD1, anti-CTLA4, nivolumab, pembrolizumab, ipilimumab, rheumatic diseases, musculoskeletal diseases.

1. INTRODUCTION

Immune Checkpoint Inhibitors (ICIs) are a new promising class of anti-tumor drugs that block negative costimulation of T-cells leading to an enhanced anti-tumor immune response. Targets of these therapies include cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand-1 (PD-L1). CTLA-4 and PD-1 are negative regulatory receptors expressed on T-cells. ICIs block the negative interactions between T-cells, antigen presenting cells and tumors, allowing positive costimulation to occur and T-cells to become activated [1].

In early trials, treatment with both CTLA-4 and PD1 inhibitors showed a remarkable benefit in promoting durable anti-tumor immune responses, and this success led to the approval by the US Food and Drug Administration (FDA) of the monoclonal antibodies ipilimumab (anti-CTLA4), nivolumab (anti-PD1), pembrolizumab (anti-PD1), atezolizumab (anti-PDL1), avelumab (anti-PDL1) and durvalumab (anti-PDL1) for therapeutic use in a variety of cancers, including melanoma, Non-Small-Cell Lung Cancer (NSCLC), head and neck squamous cell carcinoma, renal cell carcinoma, Hodgkin lymphoma, bladder cancer, Merkel cell carcinoma and microsatellite instability high or mismatch repair-deficient adult and pediatric solid tumors [2].

Notwithstanding their therapeutic promise, significant toxicity, particularly consisting in Immune-Related Adverse Events (IRAEs), has been observed with both classes of ICIs, with higher rates occurring when PD1-targeted therapy is used in combination with CTLA4-targeted therapy. IRAEs may involve any organ system, including gastrointestinal tract, endocrine glands, skin, liver, cardiovascular and pulmonary systems, and may lead to significant morbidity and, to a lesser extent, mortality (Table **1**) [3].

Musculoskeletal and rheumatic diseases are among the less frequently reported IRAEs associated to ICIs treatment, but they are burdened with significant morbidity. In this narrative review, we will summarize the current evidence of rheumatic IRAEs associated with ICIs treatment.

2. METHODS

For the purpose of this narrative review, we conducted a MEDLINE database search for the following words: “arthralgia”, “xeroftalmia”, “xerostomia”, “sicca syndrome”, “vasculitis”, “myalgia”, “myositis”, “enthesitis”, “arthritis”, “systemic lupus erythematosus”, “lupus”, “polymyalgia rheumatica”, “sarcoidosis”, “musculoskeletal”, “rheumatic” and “anti-PD1”, “anti-PDL1”, “anti-PD1 antibody”, “anti-CTLA4”, “CTLA4 antibody”, “ipilimumab”, “avelumab”, “nivolumab”, “atezolizumab”, “pembrolizumab”, “durvalu-

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Table 1. Therapeutic indications and commonly reported adverse events of the main ICIs.

Drug	ICI Target	Therapeutic Indications	Commonly Reported Adverse Events
Ipilimumab	CTLA-4	Metastatic melanoma	Fatigue, rash, colitis (+), hepatotoxicity, pneumonitis (-), hypophysitis (+), hypothyroidism
Pembrolizumab	PD-1	Metastatic melanoma, NSCLC, Head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, gastric cancer	Fatigue, rash, colitis (-), hepatotoxicity, pneumonitis (+), hypophysitis (-), hypothyroidism
Nivolumab	PD-1	Metastatic melanoma, NSCLC, Renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma	Fatigue, rash, colitis (-), hepatotoxicity, pneumonitis (+), hypophysitis (-), hypothyroidism
Atezolizumab	PD-L1	NSCLC, locally advanced or metastatic urothelial carcinoma	Fatigue, rash, hepatotoxicity, hypophysitis (+), hypothyroidism

mab", "anti-programmed death 1 monoclonal antibody", "immune checkpoint inhibitor".

3. RESULTS

Globally considered, rheumatic and musculoskeletal IRAEs appear to be rarer than other more frequent and burdensome ones, like pneumonitis, hypophysitis and colitis. In a French registry of grade ≥ 2 IRAEs occurring in 908 ICI-treated patients, 21 (2.3%) experienced an event, excluding arthralgia and myalgia, which are more commonly reported and may rather represent a manifestation of the neoplastic disease itself [4]. In another single-center registry of 400 patients treated with ICIs, only 14 (3.5%) developed rheumatic diseases [5].

Tables **2** and **3** summarize the findings of the rheumatic and musculoskeletal IRAEs occurring in the ICI-treated patient, as reported by observational studies, case series and case reports.

3.1. Arthralgia and Inflammatory Arthritis

Arthralgia is among the most commonly reported AEs, both in clinical trials, observational studies and case reports. The incidence of arthralgia is around 9-12% and 6-8% for patients receiving pembrolizumab and nivolumab, 5% for patients receiving ipilimumab and 11% for patients receiving the combination therapy of nivolumab and ipilimumab [6].

In a recent systematic review that included 33 clinical trials of all ICIs in different types of cancer, articular pain was the most commonly reported musculoskeletal complaint (1-43% of participants), whereas a true inflammatory arthritis was reported in only five trials, with a prevalence of 1-7% [1].

The same authors described 13 patients with rheumatologic events following nivolumab, ipilimumab or combination therapy. Inflammatory arthritis was seen in 9 patients, with synovitis confirmed in 4 patients by imaging techniques. Some patients required biologic treatment with etanercept, adalimumab or infliximab to achieve mostly a partial response [7].

In another retrospective chart review, the authors reported four cases of inflammatory polyarthritis, four patients with oligoarthritis and two with tenosynovitis. Six of them were ANA positive and two had anti-citrullinated protein (anti-CCP) antibodies. All patients were treated with systemic corticosteroids, even at a small dose, and five patients received steroid-sparing agents. Even so, in some of the patients, the joint symptoms persisted for months [8].

In another retrospective study, conducted in metastatic melanoma treated with pembrolizumab or nivolumab and ipilimumab, 13.3% of patients developed arthralgia. Most frequently, arthralgia involved large joints (shoulders, knees) in a predominantly symmetrical pattern. Only two patients were seropositive for rheumatoid factor and/or anti-CCP antibodies. Ten patients developed a frank inflammatory arthritis. The majority of patients was treated with Non-steroidal Anti-inflammatory Drugs (NSAIDs), 23.1% required additional low-dose corticosteroids and 7.6% of patients received immunosuppressive treatment [9].

Inflammatory arthritis may affect both large and small joints, and may present with different clinical phenotypes, sometimes as oligoarthritis, sometimes as additive arthritis but also as severe polyarthritis [7, 10].

A French retrospective study reported that a polyarthritis resembling Rheumatoid Arthritis (RA) developed in six patients receiving ICIs; all six were positive for anti-CCP antibodies and four for rheumatoid factor. The median time to the event after exposure to the drug was 1 month (range 1-9 months). Three patients needed to be treated with disease-modifying anti-rheumatic drugs (DMARDs); the others received corticosteroids or NSAIDs [11].

In the French registry including 908 patients, the prevalence of RA was very low (0.2%), whereas that of non-RA inflammatory polyarthritis was slightly higher (1.2%), reaching 2.5% when ICIs were used in combination [4]. In another single-center registry, polyarthritis was seen in 10 out of 400 patients (2.5%), oligoarthritis in one patient and monoarthritis in another one [5].

Among non-RA inflammatory arthritis, *de-novo* psoriasis and Psoriatic Arthritis (PsA) were reported to be induced by

Table 2. Published case reports and case series of musculoskeletal IRAEs induced by ICIs.

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Hunter 2009 [31]	Ipilimumab	Melanoma	Dysphagia, dysarthria, diffuse muscle weakness, elevation of CK. Diagnosis of acute polymyositis	No (symptoms appeared after the end of therapy)	Corticosteroid and intravenous Ig Response to therapy and healing of melanoma	Case report
Fadel 2009 [36]	Ipilimumab	Melanoma	After two injections, the patient developed signs and symptoms of lupus nephritis	Yes	Corticosteroid therapy with clinical improvement	Case report
Manousakis 2013 [43]	Ipilimumab	Metastatic melanoma	Asymmetric, severe weakness involving all limbs, respiration, and cranial nerves, which was progressive over 2 weeks. EMG/NCS showed an axonal polyradiculoneuropathy with multifocal motor conduction blocks. Nerve pathology showed inflammation around the endoneurial microvessels and subperineurial edema and inflammation	Yes	Improvement over months without further treatment	Case report
Minor 2013 [45]	Ipilimumab	Melanoma	Uterine lymphocytic vasculitis presenting with a mass in uterus and pelvic lymphadenopathy	No (therapy just finished)	Hysterectomy due to concern for malignancy No further treatment	Case report
Goldstein 2014 [46]	Ipilimumab	Melanoma	Two patients developed polymyalgia rheumatica w/o giant cell arteritis	Yes	High dose corticosteroid therapy After six months one patient died	Case series
Chan 2015 [17]	Pembrolizumab	Melanoma	First case: Knee arthritis Second case: Polyarthritis and myalgia diagnosed as seronegative inflammatory arthritis	Yes (in the first case drug was restarted after symptoms resolution)	First case: Steroid therapy with resolution of symptoms Second case: naproxen, hydroxychloroquine and paracetamol	Case series
Sheik 2015 [30]	Ipilimumab	Melanoma	Erythematous rash with Gottron's papules and proximal muscle weakness Diagnosis: dermatomyositis	Yes	Prednisone 80 mg daily tapered over 8 weeks. Only a minimal clinical response was achieved.	Case report
Yoshioka 2015 [27]	Nivolumab	Melanoma	Shortness of breath with CPK elevation Diagnosis: Myositis complicated by respiratory distress	Yes	Complete recovery after several weeks	Case report
Garel 2016 [48]	Pembrolizumab	Metastatic melanoma	Two patients presenting with pain of the shoulders and hip girdles, morning stiffness Diagnosis: Polymyalgia rheumatica	No (partial in one case)	Fast improvement 48 hours after the beginning of oral prednisone. Disease remission at one month	Case report
De Velasco 2016 [19]	Nivolumab	Metastatic clear cell renal cell carcinoma	Autoimmune uveitis and Jaccoud's arthropathy	Yes	Improvement of uveitis with corticosteroid treatment. Not reported the outcome of arthropathy	Case report
Khoja 2016 [35]	Pembrolizumab	Melanoma	Eosinophilic fasciitis	No (symptoms appeared after the end of therapy)	Corticosteroid therapy with clinical improvement	Case report

(Table 2) Contd…

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Law-ping-man 2016 [14]	Nivolumab	NSCLC	After eight infusion of drug, the patient developed psoriatic arthritis	Yes (for 4 weeks)	Corticosteroid and MTX therapy with improvement of skin lesions and arthritis and subsequent stop of steroid and MTX	Case report
Kimura 2016 [28]	Nivolumab	Melanoma	Two months after the first dose acute polymyositis developed	Yes	Corticosteroids, intravenous immunoglobulin, PLEX with significant benefit	Case report
Schmutz 2016 [12]	Nivolumab	NSCLC	After eight infusions, the patient developed psoriatic arthritis	Yes	Corticosteroid and MTX were started Nivolumab was restarted after response of skin lesions	Case report
Fox 2016 [25]	Nivolumab	Melanoma	After the second dose of drug, severe muscle pain, difficulty breathing, shortness of breath, and an inability to lift the legs with CPK elevation Diagnosis: Myositis	Yes	Corticosteroids with normalization of CK within one week	Case report
Vallet 2016 [34]	Pembrolizumab	Melanoma	After two injections, proximal bilateral limb weakness and dysphonia with CPK elevation Diagnosis: Myositis	Yes	Corticosteroids followed by two cycles of PLEX, followed by one PLEX per week for 3 weeks One month after the onset of symptoms, patient had a near complete clinical recovery. No relapses at 3 months of follow-up	Case report
Konoeda 2017 [21]	Nivolumab	Advanced colon cancer	Bilateral ptosis, limb and neck weakness, dyspnea, and myalgia in two weeks. Diagnosis of myasthenia gravis and myositis	Yes	Oral prednisolone, intravenous immunoglobulin and plasma exchange with noninvasive positive-pressure ventilation	Case report
Haddox 2017 [33]	Pembrolizumab	Melanoma	Progressive dysarthria, bilateral ptosis, neck weakness, dysphagia, diffuse myalgia, and mild proximal muscle weakness in both the upper and lower extremities. Diagnosis of immune-mediated necrotizing myopathy over a NMJ disorder	Yes	Prednisone and PLEX (three sessions) were started but patient continued to deteriorate and died for respiratory failure. An autopsy was performed, which revealed diffuse necrotic myositis of the diaphragm and lymphohistiocytic myocarditis	Case report
Teyssonneau 2017 [41]	Pembrolizumab	Left parotid acinic cell carcinoma with adrenal gland and lung metastases	Dry-eye syndrome, conjunctival hyperemia, xerostomia and skin rash on both hands identified as Gougerot-Sjogren like syndrome	No	Daily dose of 10 mg prednisone, betamethasone cream for the hands, artificial tear drops and artificial saliva. For dry-eye syndrome and the xerostomia, which significantly affected the patient's daily life, treatment with pilocarpine	Case report
Behling 2017 [29]	Nivolumab	Melanoma	Moderate pain in the proximal muscle groups of the upper limbs and a slight worsening of a pre-existing dyspnea (started 10 days after the first infusion). Three days later dyspnea, dysphagia, and worsened muscle pain lead to hospitalization. Increase of CPK, myoglobin, troponin I, ANA positive Diagnosis of autoimmune-induced myositis	No	Immunosuppressive therapy with iv prednisone After four days of hospitalization, a third-degree atrioventricular block with a bradycardia of 44 bpm and a systolic blood pressure up to 200 mmHg developed. The patient died after 26 days of treatment	Case report

(Table 2) Contd…

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Bernier 2017 [47]	Nivolumab	NSCLC	Diffuse joint pain that occurred suddenly. Diagnosis of polymyalgia rheumatica	Yes (Drug was restarted after resolution of joint pain in association with steroid therapy)	Good response to corticosteroid therapy	Case report
Chen 2017 [26]	Nivolumab	NSCLC	Ptosis, diplopia, drop head, and general weakness 5 days after a third drug infusion conducted to a diagnosis of nivolumab-related myasthenia and myositis	Yes	Steroid treatment with methylprednisolone 1mg/kg/d and pyridostigmine 60mg twice a day was administered beginning at admission; however, the patient's condition progressively worsened, despite treatment. Respiratory failure developed 2 weeks after admission. The patient died on day 27 after the third nivolumab infusion	Case report
Dasanu 2017 [18]	Ipilimumab	Melanoma	Swelling and pain involving the right knee with signs of synovial inflammation and an important joint effusion; moderate bilateral pleural effusions and enlarged heard silhouette; large pericardial effusion	Just completed	Steroid therapy was initiated with remarkable clinical improvement over the next 24h and then was tapered over the next six weeks with resolution of pericardial and pleural effusions two weeks later. Eight months after completing ipilimumab therapy, the right knee effusion re-accumulated and prednisone was restarted	Case report
Gauci 2017 [50]	Nivolumab	Melanoma	After three drug infusions, the patient developed a variant of polymyalgia rheumatica	Yes	Corticosteroid therapy. After achieving remission, nivolumab was recommenced without any flare of arthritis	Case report
Liu 2017 [39]	Nivolumab	NSCLC	After five months of nivolumab therapy, the patient developed subacute cutaneous lupus erythematosus	Yes	Corticosteroids, hydroxychloroquine, aspirin with improvement. Nivolumab was restarted after 5 months	Case report
Mahmoud 2017 [15]	Pembrolizumab	Melanoma	Knee inflammatory synovitis	No	Prednisone and infliximab	Case report
Pushkarevskaya 2017 [32]	Ipilimumab	Melanoma	First case: After four months diagnosis of ocular myositis Second case: After two cycles of drug diagnosis of ocular myositis	Yes	First case: Corticosteroid therapy and mycophenolate mofetil and immunoglobulin Second case: Corticosteroid therapy and mycophenolate mofetil. Both resolution of myositis	Case report
Ruiz-Bañobre 2017 [13]	Nivolumab	NSCLC	Diagnosis of psoriatic arthritis after the 11th course of nivolumab	No	Corticosteroid and NSAIDS therapy and then MTX with nivolumab. Minimal disease activity was achieved	Case report
Saini 2017 [24]	Nivolumab	Hodgkin lymphoma and then acute myeloid leukemia	Diffuse edema with subsequent diagnosis of autoimmune myositis	No	Corticosteroid therapy. The patient died after six months from diagnosis	Case report
Salmon 2017 [16]	Pembrolizumab	Melanoma	After nine infusions, the patient developed polyarthritis and fever	No	Corticosteroid therapy and then MTX were prescribed with moderate benefit	Case report

(Table 2) Contd…

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Gambichler 2017 [44]	Nivolumab + ipilimumab	Melanoma	After three weeks, the patient developed progressive erythema, paresthesia and pain on the fingertips of both hands Diagnosis: Acral vascular syndrome Histopathology did not reveal evidence for vasculitis	No	Treatment with corticosteroids and prostacyclin. The patient died for cancer progression	Case report
Firwana 2017 [54]	First case: Ipilimumab Second case: Ipilimumab Third case: Ipilimumab followed by pembrolizumab	Melanoma	First case: Tender retroauricular, occipital, cervical, and axillary lymphadenopathy. PET CT showed substantial bilateral cervical, axillary, hilar, mediastinal, iliac, and inguinal lymphadenopathy Second case: PET CT showed diffuse hilar and mediastinal lymphadenopathy. Pathology revealed multiple poorly formed epithelioid granulomas with multinucleated giant cells, focal necrotic debris, and abundant small lymphocytes, but no evidence of melanoma. Third case: The patient developed a granulomatous skin lesion on right forearm. A biopsy of the lymph node confirmed a systemic granulomatous process	First case: Yes Second case: Not reported Third case: Yes, but not immediately	First case: No corticosteroids were prescribed. Follow-up PET CT obtained three months later showed complete resolution of the lymphadenopathy Second case: Not reported Third case: Symptoms resolved spontaneously in few weeks without any treatment. PET-CT imaging obtained two months after stopping pembrolizumab showed stable lymphadenopathy	Case series
Lainez 2017 [59]	Nivolumab	NSCLC	After 8 injections of nivolumab, a new CT and PET scan revealed massive growth and increase in metabolism of hilar and mediastinal lymph nodes. EBUS-TBNA showed an epithelioid cell reaction compatible with sarcoidosis	No	Stability of disease at 12 months without treatment	Case report
Reuss 2017 [60]	Nivolumab plus ipilimumab	Metastatic melanoma	PET-CT scan revealed new supraclavicular, mediastinal, right hilar and left iliac adenopathy, as well as subcutaneous left pretibial and right calf nodules. Histology showed non-caseating granulomas. Diagnosis of sarcoidosis	Partial: Nivolumab monotherapy was maintained	Stable disease without treatment	Case report
Reddy 2017 [58]	Ipilimumab plus pembrolizumab (1 case) Ipilimumab plus nivolumab (1 case)	Metastatic melanoma	Mediastinal and hilar lymphadenopathy and multiple subcentimeter pulmonary nodules in the bilateral upper and lower lobes of the lungs and skin lesion consistent with sarcoidosis (1 case) Mediastinal and hilar lymphadenopathy as well as mild nonspecific nodularity in the right lower lung and several subcutaneous nodules that on biopsy showed a granulomatous infiltrate within the dermis and subcutaneous fat, composed of well-formed noncaseating granulomas with multinucleated giant cells and scattered lymphocytes. The final diagnosis was sarcoidosis	Yes (temporary withdrawal)	Improvement with corticosteroids	Case report

(Table 2) Contd…

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Lomax 2017 [57]	One case: Nivolumab vs ipilimumab Two cases: Pembrolizumab	Melanoma	Hilar and mediastinal adenopathy and subcutaneous nodules. Diagnosis of sarcoidosis	Yes (2 cases) No (1 case)	No treatment (1 case) with improvement Corticosteroid therapy (2 cases) with improvement	Case series
Zhang 2017 [56]	Nivolumab	Metastatic clear cell renal carcinoma	PET CT showed asymptomatic bilateral mediastinal and hilar lymphadenopathy. Histopathology examination revealed epithelioid granulomas consistent with sarcoidosis	Not reported	Not reported	Case report
Nakamagoe 2017 [49]	Nivolumab	Metastatic melanoma	After 2 months, generalized joint pain and weakness of proximal muscles developed. A diagnosis of polymyalgia rheumatica was made	Yes	Oral corticosteroid with marked improvement with 24 hours and resolution of symptoms after 3 weeks	Case report
Tan 2017 [23]	Nivolumab	NSCLC	Immune-mediated myasthenia gravis and myositis with respiratory failure	No	Treatment with pyridostigmine, methylprednisolone (1 g daily for 3 days), and immune globulin (400 mg/kg/d for 5 days) with benefit	Case report
Aya 2017 [42]	Pembrolizumab	Melanoma	Bilateral paresthesia in glove and stocking distribution that rapidly progressed with severe weakness in her lower limbs and diplopia (6th cranial nerve palsy). Electromyography and nerve conduction study showed a moderate sensory peripheral polyneuropathy. Muscle and nerve biopsy showed some angulated atrophic muscle fibers and perivascular infiltration of mononuclear cells of small endoneural vessels	Yes	Pulses of corticosteroids, then oral prednisone at 1 mg/kg slowly tapered over 6 months until 5 mg/day and then discontinued. Complete functional recovery over 6 months.	Case report
Nandavaram 2017 [52]	Ipilimumab	Melanoma	Asymptomatic mediastinal and hilar nodes bilaterally. Histopathological examination revealed non-caseating granulomatous lymphadenitis characterized by aggregates of epithelioid macrophages consistent with sarcoidosis	Yes	Improvement without further treatment	Case report
Kim 2017 [62]	Ipilimumab Pembrolizumab	Metastatic melanoma	Three cases of symmetric polyarthritis involving small joints that developed between the second and the fourth infusion of the drug	No	All patients received corticosteroids and IL-6 receptor antagonist (tocilizumab) with articular response. One patient discontinued tocilizumab because of adrenal insufficiency	Case series
Shao 2018 [38]	Pembrolizumab	Melanoma	Erythematous and non-pruritic eruption of edematous papules coalescing into plaques on his back, chest, lateral arms, thighs, and abdomen Histological findings of papules were interpreted as a lupus-like medication reaction	Yes	Within one month, the rash completely resolved without use of topical steroids or other topical medications	Case report

(Table 2) Contd…

References	Drug	Indication	Clinical Presentation	Withdrawal of Drug	Treatment and Outcome	Type of Study
Yatim 2018 [55]	Pembrolizumab	Melanoma	PET/CT-scan found at the thoracic level bilateral new multiple pleural and parenchymal hypermetabolic lesions and hypermetabolic enlarged bilateral hilar lymph nodes and multiple subcutaneous highly metabolic active nodules appeared on the left flank, right leg, hypogastric region and on a laparotomy surgical scar. Bilateral anterior uveitis was present. The patient was diagnosed with sarcoidosis	No (after the end of therapy)	No treatment. Three months later another PET/CT-scan showed complete regression of the hypermetabolic sarcoidosis lesions	Case report

nivolumab in a few patients with advanced lung cancer [12, 13]. Some of the authors speculated that the induction of psoriasis may correlate with the therapeutic activity of nivolumab, since the occurrence of the psoriatic skin lesions as well as joint symptoms temporally coincided with the regression of lung cancer lesions [14]. In all the cases the patients received corticosteroids and methotrexate with significant benefit.

Pembrolizumab induced a recurring monoarthritis of both knees in a woman with metastatic melanoma [15] but was also responsible for the acute onset of polyarticular inflammatory arthritis [16, 17]. In two of these patients, pembrolizumab caused a severe polyarthritis after 14 and 11 months of therapy, respectively. The first patient had tenosynovitis, synovitis, bone marrow edema, and myositis, whereas the second patient had predominantly synovitis and tenosynovitis. Remission of symptoms was obtained with bisphosphonates and salazopyrin.

In a patient treated with ipilimumab for metastatic melanoma, acute monoarthritis of the knee with a large effusion developed two months after completing ICI therapy and recurred eight months after treatment discontinuation. At both occasions, the patient was given systemic corticosteroid with a moderate benefit. The same patient had pericardial tamponade and bilateral pleural effusions that improved with steroid treatment [18].

A patient treated with nivolumab developed autoimmune uveitis and Jaccoud's arthropathy. The drug was discontinued and uveitis was treated with intraocular steroids with success, but the treatment strategy of the joint disease was not reported [19].

Given the extreme variability of clinical presentations and patterns of inflammatory arthritis in patients receiving ICIs, some authors speculated that one group of patients may develop non-specific arthritis due to the up-regulation of the immune system and another group may develop a more specific form of arthritis, like RA or PsA, based on a genetic or environmental predisposition [20].

3.2. Myalgia and Inflammatory Myositis

Myalgia was the second most commonly reported musculoskeletal complaint in clinical trials (2-21% of trial participants) [1]. Nevertheless, several cases of true inflammatory myositis have been described, especially with anti-PD1 treatment.

Treatment with nivolumab has been associated with the development of myositis and myocarditis, even of the severe entity, in a number of case reports and case series, especially in Eastern Asia [21-25]. A patient treated with nivolumab for advanced colon cancer received a diagnosis of myasthenia gravis and myositis for bilateral ptosis, limb and neck weakness, dyspnea and myalgia developing in two weeks. The patient improved after drug withdrawal and prednisolone and intravenous immunoglobulin administration. Another patient developing severe muscle pain, weakness and shortness of breath after the second dose of nivolumab rapidly improved with drug discontinuation and prednisone administration. In the largest retrospective study, among 12 patients with myasthenia gravis, 4 had concomitant myositis and 3 had myocarditis, with 1 of these patients having both.

In these cases of nivolumab-induced myositis, drug withdrawal and corticosteroid with or without further immunosuppressive therapy were usually effective. Respiratory muscle involvement appeared to be the most fearful complication of nivolumab-induced myositis, causing the death of the patient in one case, even though in another case an improvement was seen after drug discontinuation and corticosteroid administration [26, 27].

Though IRAEs usually present after some months after drug inception, the onset of severe myositis and myocarditis has been described even after only one dose of nivolumab. This patient improved with corticosteroid treatment, intravenous immunoglobulin and plasma exchange after drug discontinuation [28].

Finally, nivolumab was also found to induce an autoantibody-positive myositis and myocarditis complicated with a new-onset third-degree atrioventricular block [29].

Ipilimumab-induced dermatomyositis has been described in a patient with metastatic melanoma. The clinical picture included erythematosus rash with Gottron's papules and proximal muscle weakness. The drug was discontinued and prednisone 1 mg/kg was started, with minimal clinical response [30].

Another patient developed severe autoimmune myositis following ipilimumab administration, presenting with dysphagia, dysarthria, diffuse muscle weakness and CK elevation. She was treated with intravenous immunoglobulin (400/mg/kg) for ten days and high dose methylprednisolone followed by oral prednisone (1mg/kg daily), with significant benefit and no cancer recurrence [31].

Ipilimumab has also been associated with the development of severe ocular myositis in two patients with metastatic melanoma. In both cases, the condition improved with the administration of methylprednisolone, mycophenolate mofetil and, in one patient, intravenous immunoglobulin [32].

A case of pembrolizumab-induced severe bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm was described in a 78-year-old man with metastatic melanoma. This patient developed progressive dyspnea, bilateral ptosis, neck and limb muscle weakness and dysphagia. Prednisone and plasma exchange did not improve his condition and he died for respiratory failure. Interestingly, the autopsy revealed a diffuse necrotic myositis of the diaphragm and a lymphohistiocytic myocarditis [33].

Other authors reported a case of pembrolizumab-induced myositis, with the muscle biopsy showing multifocal necrosis with adjacent endomysial CD8+ T cell predominant infiltrates, without inclusion bodies. Pembrolizumab was discontinued and the patient was treated first with corticosteroids and then with plasma exchange due to intolerance. The patient experienced a near complete clinical recovery after one month [34]. Among rarer IRAEs, eosinophilic fasciitis has been reported following pembrolizumab treatment in a patient with metastatic melanoma [35].

Myositis was also described in a patient receiving dual treatment with tremelimumab and durvalumab for non-small cell lung cancer. The complication arose in about one month and corticosteroid treatment provided moderate benefit [10].

3.3. SLE and Sicca Syndrome

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that may involve several organ systems, including skin, joints, heart, lungs, nervous system and kidneys. In our literature review, SLE was rarely found to be associated with ICIs treatment, particularly with ipilimumab.

The first case of lupus-nephritis induced by ipilimumab was described in 2009 in a patient treated for metastatic melanoma. The kidney biopsy showed immunoglobulin and complement complexes in the mesangial space and the serum anti-double-stranded-DNA antibody test was positive, before treatment with prednisone and ipilimumab discontinuation that eventually improved the nephritis [36].

In a large registry, induction of SLE was reported in only one patient among 524 that experienced an IRAE while on ipilimumab treatment [37].

A lupus-like cutaneous reaction in the setting of pembrolizumab therapy for metastatic melanoma was described [38], as well as in a patient receiving nivolumab for metastatic lung cancer [39]. In the latter case, erythematous and non-pruritic papules developed, with histological findings suggestive of a lupus-like drug reaction. The skin rash improved after one month without further treatment other than nivolumab discontinuation.

Dry eyes and dry mouth have been reported as mild AEs in some ICIs clinical trials, with an incidence ranging from 3-24% [1, 40]. In a large French registry reporting only grade ≥ 2 IRAEs occurring in ICI-treated patients, the prevalence of true Sjogren's syndrome was 0.3% [4].

Four out of five patients with sicca syndrome described in a retrospective study had dry mouth without eye involvement following nivolumab, atezolizumab or combination treatment. ANA was positive in two of the five patients, and SSA was positive in one [10].

In another case series, four patients presented sicca symptoms with severe salivary hypofunction developing on nivolumab, ipilimumab or combination therapy. On ultrasound imaging, one patient had discrete hypoechoic foci occupying more than 50% of her parotid and submandibular glands, as it is usually seen in Sjogren's syndrome. One patient had also pneumonitis and another had interstitial nephritis and colitis. Three of four sicca patients had positive ANA; one patient had low titre La/SSB antibodies; none of the patients had Ro/SSA antibodies [7].

A patient with metastatic parotid carcinoma developed a sicca syndrome associated with a skin rash on both hands that was identified as Gourgerot-Sjogren like syndrome [41].

3.4. Vasculitis

Isolated cases of vasculitis have been reported following the administration of ICIs (ipilimumab in 3 cases, pembrolizumab in 2 cases) in a large biologic drug registry [37]. Most cases of vasculitis induced by biologics present with isolated cutaneous or neurological (peripheral neuropathy) involvement, and systemic vasculitis appear to be rare. Only two clinical trials of ICIs reported the onset of vasculitis among patients receiving these compounds and in one case a giant cell arteritis was diagnosed [1].

Among isolated vasculitis, cases of peripheral neuropathy due to histologically proven small vessel vasculitis have been reported. One was induced by pembrolizumab in a 53-year-old woman with seropositive RA and metastatic melanoma. She was treated with high-dose corticosteroids, followed by a gradual tapering, with a complete functional recovery over 6-months and minimal residual paraesthesia [42].

Even though not all cases of asymmetric polyradiculoneuropathy described in patients on ICIs are secondary to vasculitis, an aspecific microvasculopathy underlying the pathogenesis of the nerve damage has been occasionally described [43], as well as an acral vascular syndrome presenting with progressive erythema, paresthesia and fingertip pain, but without histological evidence of vasculitis [44].

Another isolated form of vasculitis involved the uterine circulation, with lymphocytic infiltration and focal fibrin deposition. This patient was receiving ipilimumab for metastatic melanoma and presented with an asymptomatic uterine mass [45].

Table 3. Published observational studies reporting the incidence of musculoskeletal IRAEs in ICI-treated patients.

References	Drugs	Indications	Clinical Presentation	Withdrawal of Drugs	Treatment and Outcome	Type of Study
Smith 2017 [8]	Nivolumab Pembrolizumab Ipilizumab Tremelimumab	Melanoma NSCLC Anal cancer Cervical cancer Merkel cell carcinoma Renal cancer	Ten patients, seven treated with combination therapy and 3 in monotherapy 4 cases of polyarthritis 4 cases of oligoarthritis 2 cases of tenosynovitis of which: 6 were ANA positive 2 were anti-CCP positive	No (except one case)	All patients were treated with systemic corticosteroids for their arthritis or tenosynovitis Three patients were started on DMARDs and one patient required infliximab to allow tapering of steroids Six of the patients had resolution of musculoskeletal symptoms and discontinued treatment an average of 9.2 months after the last dose of immunotherapy Four patients continued to be treated for their arthritis at the time of last rheumatology follow up	Retrospective study
Le Burel 2017 [4]	Nivolumab Nivolumab + Ipilimumab Pembrolizumab Atezolimumab Durvalumab	Melanoma Colon and gastric adenocarcinoma Renal cell cancer Lung cancer Cervical and urothelial carcinoma Brain glioblastoma	Out of 908 patients, 30 patients experienced systemic immune-related adverse events: 4 cases of immune cytopenia (including 3 cases of immune thrombocytopenia) 10 with connective tissue diseases (4 cases of Sjogren syndrome, 3 cases of rheumatoid arthritis, and 3 cases of myositis), 14 with other inflammatory arthritic conditions (including 4 cases of polymyalgia rheumatica, 3 cases of psoriatic arthritis, and 7 cases of seronegative polyarthritis), and 2 with sarcoidosis	Yes (in 12 cases)	25 patients (83%) received corticosteroids, and five patients (17%) received immunomodulatory agents (corticosteroid + MTX or iv immunoglobulin) Once the IRAEs had been detected, the symptoms disappeared in 13 patients (43%), decreased in 15 patients (50%), remained stable in 2 patients (7%) and worsened in none	French Registry Retrospective Study
Pérez-De-Lis 2017 [37]	Ipilimumab (524) Tremelimumab (2) Nivolumab (225) Pembrolizumab (162)	Not declared	Lupus in 1 patient treated with ipilimumab Vasculitis in 3 patients treated with ipilimumab; 2 patients treated with pembrolizumab. Sarcoidosis in 13 patients treated with ipilimumab; 3 patients treated with pembrolizumab; 4 patients treated with nivolumab Rheumatoid arthritis in 6 patients	Not declared	Not declared	Retrospective study from BIO-GEAS Registry
Suzuki 2017 [22]	Nivolumab Ipilimumab	Melanoma Lung cancer Colon cancer	Twelve myasthenia gravis cases (0.12%) among 9869 patients with cancer who had been treated with nivolumab, but none among 408 patients treated with ipilimumab	Yes	Immunosuppressive therapy: High dose corticosteroid therapy, iv immunoglobulin, and plasma exchange	Retrospective study
Belkhir 2017 [11]	Nivolumab Pembrolizumab Anti-PDL1	Melanoma Endometrial and vagina adenocarcinoma Lung adenocarcinoma Gastric and colon carcinoma	10 patients developed: Rheumatoid arthritis in 6 cases; polymyalgia rheumatica in 4 cases	No (except one case)	Patients with rheumatoid arthritis: 3 treated with DMARDS (with good response) and 3 with steroid or NSAIDS (with resolution of symptoms) Patients with polymyalgia rheumatica were treated with steroid therapy with resolution of symptoms	Retrospective study

(Table 3) Contd…

References	Drugs	Indications	Clinical Presentation	Withdrawal of Drugs	Treatment and Outcome	Type of Study
Calabrese 2017 [10]	Nivolumab+ ipilimumab (7) Ipilimumab + pembrolizumab (1) Nivolumab (5) Atezolimumab (1) Durvalumab (1) Tremelimumab (1)	Melanoma NSCLC Renal cell carcinoma	15 patients developed: sicca syndrome in 5 cases, arthritis in 7 cases, myositis in 1 case and polymyalgia rheumatica in 3 cases. Lab tests showed: ANA positivity in 4 cases FR positivity in 11 cases Anti-SSA positivity in 1 case Anti-dsDNA positivity in 1 case	Yes (in 12/15 patients)	Corticosteroid therapy Infliximab in 2 cases Etanercept in 2 cases Adalimumab in 1 case Methotrexate in 2 cases These treatments led to significant improvement in 6 patients, moderate improvement in 5 patients and only minimal improvement in 2	Single center retrospective study
Cappelli 2017 [7]	Nivolumab + ipilimumab (8) Nivolumab or ipilimumab (5)	Melanoma NSCLC Renal cell carcinoma	13 patients developed: Sicca syndrome in 4 cases; arthritis in 9 cases ANA were positive in 5 out of 13 patients	Yes	These therapies were performed: Corticosteroid therapy Infliximab in 2 cases; Etanercept in 1 case; Adalimumab in 3 cases; NSAIDS as needed Outcome: stable disease in 5 cases; partial response in 6 cases; progressive disease in 1 case; non measureable in 1 case	Retrospective study
Tetzlaff 2018 [53]	Ipilimumab (14) Nivolumab (3) Pembrolizumab (5) Ipilimumab + nivolumab (3) Anti-PD-L1 (1)	Melanoma Prostate adenocarcinoma NSCLC Hodgkin lymphoma Ovarian cancer Colorectal carcinoma	A review of 26 patients (including the 3 from this report) who developed granulomatous/sarcoid-like lesions are described	Yes (in 10/26 patients)	Systemic steroids in 12 patients (44%) Outcome of sarcoidosis: Resolution in 14 cases; Improvement in 9 cases; Stable in 1 case; Not reported in 2 cases. Disease response to ICI: Stable in 5 cases; Remission in 10 cases; Progression in 6 cases; Not reported in 5 cases	Retrospective study and literature review
Kostine 2017 [61]	Nivolumab Pembrolizumab Atezolizumab Avelumab Anti-PD1+anti-CTLA4 (5)	Melanoma Merkel carcinoma NSCLC Renal cancer	35 (6.6%) out of 524 ICI-treated patients were referred to the Rheumatology Clinic. Inflammatory arthritis occurred in 20 cases (3.8%), with 7 cases mimicking rheumatoid arthritis, 11 cases PMR, 2 cases psoriatic arthritis	No (except one case)	All patients required corticosteroids (max 30 mg/day), leading to clinical improvement or remission. Two patients required DMARDs (MTX). After 6 months, 2 patients were able to discontinue corticosteroids	Single center prospective observational study
Lidar 2018 [5]	Nivolumab (4) Ipilimumab (1) Ipilimumab + nivolumab (1) Pembrolizumab (8)	Melanoma Endometrial cancer Sinonasal cancer Hodgkin's lymphoma Breast cancer	Polyarthritis in 10 cases Oligoarthritis in 1 case Monoarthritis in 1 case Sarcoidosis in 1 case Eosinophilic fasciitis in 1 case	No (3 cases) Withheld (3 cases) Off therapy (8 cases)	NSAIDS (11 cases) Steroid therapy (14 cases) MTX (8 cases) Outcomes: Low disease activity (9 cases) Moderate (1 case) Remission (3 case) Unknown (1 case)	Single center registry

(Table 3) Contd….

References	Drugs	Indications	Clinical Presentation	Withdrawal of Drugs	Treatment and Outcome	Type of Study
Buder-Bakhaya 2018 [9]	Pembrolizumab or Nivolumab ±Ipilimumab	Melanoma	195 patients were included 26 patients developed arthralgia (mainly large joints). Of these, 2 were FR ± anti-CCP positive, 10 developed arthritis and 5 progressive osteoarthritis. In 11 patients, arthralgia could not be specified	Yes, in 7.7% of patients	The majority of patients (73.1%) received NSAIDs with benefit 5 patients (19.2%) further needed low-dose prednisolone. A patient with RA additionally received sulfasalazine and hydroxychloroquine. Outcomes: 5 patients were able to stop NSAIDs ± low dose prednisolone completely, 6 patients still require NSAIDs ± low dose steroids	Retrospective study

3.5. Polymyalgia Rheumatica

Polymyalgia Rheumatica (PMR) almost invariably responds to systemic corticosteroids, even if occurring in patients receiving ICIs.

Some authors reported the development of PMR in two patients with metastatic melanoma being treated with ipilimumab. In one case, a biopsy of the right temporal artery was performed, showing active arteritis, intimal proliferation, and disruption of the internal elastic lamina. Both patients had a brisk response to corticosteroids, with improvement in symptoms and indices of inflammation [46].

In a French retrospective study, PMR was diagnosed in four patients treated with pembrolizumab and nivolumab ± ipilimumab, and all patients responded to treatment with corticosteroids [11].

Another French group reported the development of PMR in a patient with non–small cell lung cancer after 13 cycles of nivolumab, with a good response to corticosteroid therapy [47].

In a case series from the Cleveland Clinic, 3 out of 15 patients evaluated at the Rheumatology Unit had clinical characteristics compatible with PMR including pain and stiffness involving the shoulders, hips and neck, with associated severe morning stiffness. None of them had symptoms concerning for giant cell arteritis [10]. Other patients receiving nivolumab and pembrolizumab developed typical features of PMR that responded well to corticosteroid treatment [48, 49].

Finally, other authors described a variant of PMR, called remitting seronegative symmetrical synovitis with pitting edema syndrome, to be induced by nivolumab in an 80-year-old man with metastatic melanoma [50].

3.6. Sarcoidosis

Several cases of new-onset sarcoidosis were reported in patients being treated with ICIs for metastatic melanoma, including those from a large biologic drugs registry in which sarcoidosis complicated treatment with ipilimumab (13 cases), nivolumab (4 cases) and pembrolizumab (3 cases) [37]. In another retrospective study, 5% out of 147 patients undergoing ipilimumab treatment for melanoma developed sarcoid-like lymphadenopathy after a median interval time of 3.2 months from the start of ipilimumab. The majority of patients had mediastinal and hilar lymphadenopathy except for one patient who had a coexistent intra-abdominal lymphadenopathy [51]. Conversely, in a single center registry, the prevalence of sarcoidosis in patients receiving ICIs was very low (0.2%) [4].

Notably, some authors observed that in a patient with ICI-induced sarcoidosis the suspension of the drug alone achieved the complete resolution of the metabolically active lymph nodes without the need of additional steroid treatment [52]. Recently, some authors reviewed the cases of 26 patients developing granulomatous/sarcoid-like lesions associated with ICIs. Treatment was discontinued in 38% of patients and only 44% of the patients were treated with systemic steroids. Almost all of the patients demonstrated either resolution or improvement of granulomatous/sarcoid-like lesions irrespective of medical intervention [53].

In other three cases of ICI-related sarcoidosis-like lymphadenopathy, two occurring during adjuvant ipilimumab for stage III surgically resected melanoma and one during pembrolizumab for metastatic melanoma, histopathological examination revealed non-caseating granulomas. Two of the patients improved with drug discontinuation alone without the need of corticosteroid treatment [54]. Another melanoma patient developed sarcoidosis with bilateral anterior uveitis [55].

Several other reports confirm that sarcoid-like reactions induced by ICIs are common and often do not require other treatment than drug discontinuation [56-58], though in some cases ICI-treatment may be continued without a significant impact on the patient's clinical conditions [59, 60].

4. DISCUSSION

Our review suggests that, though rare, musculoskeletal and rheumatic diseases appear to be associated with ICI-treatment and demand a prompt recognition to avoid further impact on morbidity and mortality for cancer patients. The approach to the management of these patients may require a tight cooperation between the oncologist and the rheumatologist, that should balance risks and benefits of continuing or withdrawing anti-tumor treatment and evaluate the need for a systemic anti-inflammatory or immunomodulating therapy.

It is difficult to estimate the true incidence and prevalence of musculoskeletal AEs in patients receiving ICIs, given that most of the observational studies are retrospective. Overall, rheumatic complications appear to involve no more than 10% of the ICIs-treated patients. Most of the AEs are mild-to-moderate, except for the more severe forms of myositis that may lead to death due to respiratory involvement.

There are different treatment options for musculoskeletal AEs that vary with the extent and the severity of the disease. Inflammatory arthritis may respond to relatively short courses of NSAIDs or glucocorticoids, but some of the patients may need DMARDs and/or biologic treatment due to refractoriness or disease recurrence upon treatment tapering or discontinuation [61, 62]. PMR usually responds to glucocorticoid treatment that may be tapered as it is usually done in non-cancer patients. Severe forms of myositis may require intravenous immunoglobulin and plasma exchange in addition to corticosteroid treatment. Sarcoidosis and sarcoid-like reactions are usually managed with treatment discontinuation and glucocorticoids.

Even if mild AEs may be managed with drug discontinuation alone, continuing ICI treatment is possible and appears to be safe. Rather, patients that experienced rheumatic AEs while on ICIs showed a higher tumor response rate compared to those who did not [61]. There are several studies reporting the positive association of the tumor response rate with the incidence of different IRAEs in cancer patients [63].

Since most of the clinical trials of ICIs excluded patients with a preexisting autoimmune disease, little is known about how these drugs may affect this group of patients. Available data on immunotherapy in melanoma patients with preexisting autoimmune diseases are mostly retrospective. Among 30 patients with a variety of autoimmune diseases (from RA to inflammatory bowel diseases) treated with ipilimumab for melanoma, only 8 (27%) had an exacerbation of their autoimmune disease; all flares were medically treated and were observed within the first 6 weeks after the beginning of therapy [64]. A similar retrospective study analyzed melanoma patients who were treated with pembrolizumab or nivolumab after previous failed or intolerant treatment with ipilimumab. Twenty (38%) patients developed a flare of their autoimmune disorder requiring immunosuppression, including seven out of 13 patients with RA. The majority of the flares were relatively mild and only two patients required discontinuation of anti-PD1 treatment [65].

As far as we know, ICIs administration in a patient with a preexisting autoimmune condition is safe enough to warrant treatment. Rheumatic or autoimmune disease flares can usually be managed only with steroids, with or without discontinuation of the treatment drug, though rarely they may require immunosuppressive treatment [66, 67].

CONCLUSION

Immune checkpoint inhibitor treatment has been a breakthrough option in several metastatic cancers. As their use is increasing, there is gathering evidence that they may induce rheumatic and musculoskeletal disorders or cause disease flares in patients with a preexisting autoimmune disorder. A rapid recognition and a prompt treatment, possibly with a rheumatologist referral, may help to improve the quality of life of these complicated cancer patients.

LIST OF ABBREVIATIONS

ICIs	=	Immune Checkpoint Inhibitors
CTLA-4	=	Cytotoxic T-lymphocyte Associated Protein-4
PD-1	=	Programmed Cell Death Protein-1
PDL-1	=	Programmed Death Ligand-1
NSCLC	=	Non-small Cell Lung Cancer
IRAEs	=	Immune-related Adverse Events
NSAIDs	=	Non-steroidal Anti-inflammatory Drugs
RA	=	Rheumatoid Arthritis
DMARDs	=	Disease-modifying Anti-rheumatic Drugs
PsA	=	Psoriatic Arthritis
SLE	=	Systemic Lupus Erythematosus
PMR	=	Polymyalgia Rheumatica

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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