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Article *in* Immunotherapy · November 2017

DOI: 10.2217/imt-2017-0108

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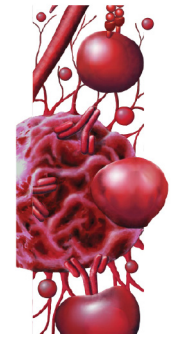

Immune-related musculoskeletal toxicities among cancer patients treated with immune checkpoint inhibitors: a systematic review

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Aim: Immune-related musculoskeletal toxicities are uncommon but potentially serious adverse events; and they may accompany the use of immune checkpoint inhibitors (ICIs). The objective of this systematic review is to assess the patterns of these musculoskeletal toxicities. **Methods & results:** PubMed database has been searched till May 2017. Clinical studies and case reports reporting the occurrence of immune-related musculoskeletal toxicities (other than arthralgia and myalgia) in cancer patients treated with ICIs were included. Eight trials with 2263 participants were included. Likewise, nine case reports reporting the outcomes of 12 patients were included. **Conclusion:** Immune-related arthritis and myositis occur uncommonly in cancer patients treated with ICIs. Further studies are required to better describe the pathogenesis as well as the time course of these events.

First draft submitted: 7 August 2017; Accepted for publication: 11 September 2017; Published online: 25 October 2017

Keywords: arthritis • atezolizumab • nivolumab • pembrolizumab

Background

Immune checkpoints work as braking system for the immune response of T cells. The two most clinically relevant subtypes of immune checkpoints include: CTLA-4 and PD-1 [1]. Upon contact of immune checkpoints to their specific ligands, these receptors exert a suppressive action on the T cells [2,3]. Immune checkpoint inhibitors (ICIs) target these regulatory receptors with the aim of releasing T cells from suppression. This shall help avoid immune evasive mechanisms of malignant tumors.

The interest has grown recently in ICIs as anticancer agents. Extensive research was conducted over the past few years evaluating their efficacy outcomes in the management of a variety of cancers [4–6]. Likewise, the safety profile of ICIs generated considerable research interest [7–11].

Among ICIs, ipilimumab and tremelimumab are CTLA4 inhibitors; while nivolumab, pembrolizumab and atezolizumab are PD-(L)1 inhibitors. These agents are the most widely studied till now [9,12–14]. Some of these agents were already approved for the treatment of some cancers like advanced melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, urothelial cancer, head and neck cancer and Hodgkin's lymphoma [4,6,12,14–18]. Moreover, an extensive research program is currently ongoing to evaluate their role in the treatment in many other solid and hematological tumors [9,11,19–21].

Why it is important to do this review?

The innovative mode of action of ICIs did not come without a price. It carried with it a completely different set of adverse events which are collectively called immune-related adverse events (IRAEs). The most commonly

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encountered IRAEs include skin, gastrointestinal, endocrine, pulmonary and hepatic adverse events [22–29]. Some less common IRAEs were also reported including rheumatologic, cardiac, ocular and neurological IRAEs [30,31]. In particular, the pattern of rheumatologic IRAEs needs to be adequately assessed as it may lead to significant morbidity and sometimes mortality.

Objective

To assess the patterns of potentially immune-related musculoskeletal toxicities (other than arthralgia and myalgia) among cancer patients treated with ICIs.

Methods

Criteria for considering studies for this review

Clinical studies, case series or reports evaluating ICIs in cancer patients and reporting the occurrence of musculoskeletal toxicities (with a probable immune etiology) were included. The possible immune etiology is determined by the authors of the primary publication and/or authors of the systematic review. Studies and case reports reporting only arthralgia and/or myalgia were not included into this review because of the high probability that these toxicities were caused by the tumor itself or other medical conditions (i.e., nonimmune related).

Types of participants included patients with any type of cancer; while evaluated interventions included ICIs (including pembrolizumab, nivolumab, atezolizumab, ipilimumab and tremelimumab). The outcomes of interest were musculoskeletal toxicities with possible immune-related etiology (namely: arthritis, myositis and myopathy). The grading of these toxicities was done through common terminology criteria of adverse events (CTCAE).

Search methods for identification of studies

PubMed database was searched till May 2017. Search terms were ('ipilimumab' [Supplementary Concept] OR 'ipilimumab' [All Fields]) OR ('tremelimumab' [Supplementary Concept] OR 'tremelimumab' [All Fields]) OR ('pembrolizumab' [Supplementary Concept] OR 'pembrolizumab' [All Fields]) OR ('nivolumab' [Supplementary Concept] OR 'nivolumab' [All Fields]) OR atezolizumab (All Fields).

Data collection & analysis

The review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [32]. The authors identified the potential records to be included. After excluding duplicate records, abstracts of the remaining publications were evaluated. A data extraction form was used to get out the necessary data. This form included the following: publication year/study authors, study design, treatment indication and outcomes (musculoskeletal toxicities). Because of lack of homogeneity of the data, the outcomes of the review were not meta-analyzable.

Results

Results of the search

Three thousand and twenty-seven publications were identified from the database search as well as from other searches. Among identified records, the number of duplicates removed was 973 references. So, the final number of records that were scanned further was 2054 records. Based on titles and abstracts, 2011 citations were excluded. Therefore, 43 full text papers were retrieved (Figure 1). Based on the full papers, eight prospective trials were found to be eligible and they were included [33–40]. Additionally, nine case reports/series were found to be eligible and they were included [41–49].

Included prospective trials

Eight trials were included and analyzed in this systematic review (Table 1). These trials included 2263 participants. Among the included trials in the systematic review, there were:

- Ipilimumab: one Phase II study in the adjuvant treatment of high-risk melanoma recruiting 75 patients.
- Tremelimumab: one Phase II study in the management of hepatitis C virus-related hepatocellular carcinoma recruiting 21 patients.
- Nivolumab: one Phase II study in the management of recurrent classical Hodgkin lymphoma post autologous stem cell transplantation recruiting 80 patients.

Table 1. Baseline characteristics of included trials evaluating immune checkpoint inhibitors and reporting on potentially immune-related musculoskeletal toxicities.

Study (year)	Study type	Number of patients	Immune checkpoint inhibitor dose	Indication	Musculoskeletal toxicities
Ipilimumab studies					
Sarniak *et al.* (2011)	Phase II trial	n = 75 patients	Ipilimumab every 6–8 weeks for 1 year. The first 25 patients received 3 mg/kg of ipilimumab, and an additional 50 patients received 10 mg/kg	Resected stage IIIC/IV melanoma, To determine safety and feasibility of adjuvant ipilimumab following resection ofhigh-risk melanoma	Arthritis/arthralgia All grade: 17 (22%) High grade: 2 (2%)
Nivolumab studies					
Younes *et al.* (2016)	Single-arm, Phase II trial	n = 80 patients	Patients were given nivolumab iv. over 60 min at 3 mg/kg every 2 weeks until progression, death, unacceptable toxicity or withdrawal from study	Recurrent classical Hodgkin'slymphoma who had failed to respond to autologous stem-cell transplantation and had either relapsed after or failed torespond to brentuximab vedotin, and with an Eastern Cooperative Oncology Group performance status score of 0 or 1	Arthritis All grade: 1 (1%) High grade: 1 (1%)
Tremelimumab studies					
Sangro *et al.* (2013)	Single-arm, Phase II	n = 21 patients	Tremelimumab at a dose of 15 mg/kg iv. every 90 days was administered until tumor progression or severe toxicity	Inoperable HCC confirmed by biopsy or non-invasive criteria and chronic HCV infection, their functional status was Child-Pugh class A or B	Arthritis All grade: 1 (5%) High grade: 0
Pembrolizumab studies					
Plimack *et al.* (2017)	Nonrandomized, open-label, Phase Ib study	n = 33 patients with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic urothelial cancer. Patients were PD-L1 positive	Enrolled patients received 10 mg/kg iv. pembrolizumab every 2 weeks until documented disease progression, intolerable toxic effects, intercurrent illnessprecluding further treatment or completion of 24 months of study treatment	PDL-1 positive locally advanced or metastatic urothelial cancer	Myositis All grade: 2 (6%) High grade: 1 (3%) Rhabdomyolysis All grade: 1 (3%) High grade: 1 (3%)
Robert *et al.* (2014)	Randomized Phase I	173 patients received pembrolizumab low dose (n = 89) or high dose (n = 84)	Arm A: pembrolizumab 2 mg/kg Arm B: pembrolizumab 10 mg/kg	Ipilimumab refractory advanced melanoma	Myositis: 0 vs 2 (0.7%) vs 1 (0.4%)
Reck *et al.* (2016)	Phase III	305 patientswere randomized to receive either pembrolizumabor the investigator's choice of platinum-basedchemotherapy	Pembrolizumab (at a fixed dose of 200 mg every 3 weeks)	Previously untreated advanced NSCLC	Myositis: 3 (1.9%) vs 0
Herbst *et al.* (2016)	Phase III	1034 patients were randomized: 345 allocated to pembrolizumab 2 low dose, 346 allocated to pembrolizumab high dose and 343 allocated to docetaxel	Pembrolizumab low dose: 2 mg/kg Pembrolizumab high dose: 10 mg/kg	Previously treated advanced NSCLC	Myositis: 2 (1%) vs 1 (1%) vs 1 (1%)
Bellmunt *et al.* (2017)	Phase III	542 patients were randomized to receive pembrolizumabor the investigator's choice of chemotherapy	Pembrolizumab (at a dose of 200 mg every 3 weeks)	Second-line therapy for advanced urothelial carcinoma	Myositis: 0 vs 1 (0.4%)

All grade: Grade 1–4; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; High grade: Grade 3–4; iv.: Intravenously; NSCLC: Non-small-cell lung cancer; RCT: Randomized controlled trial.

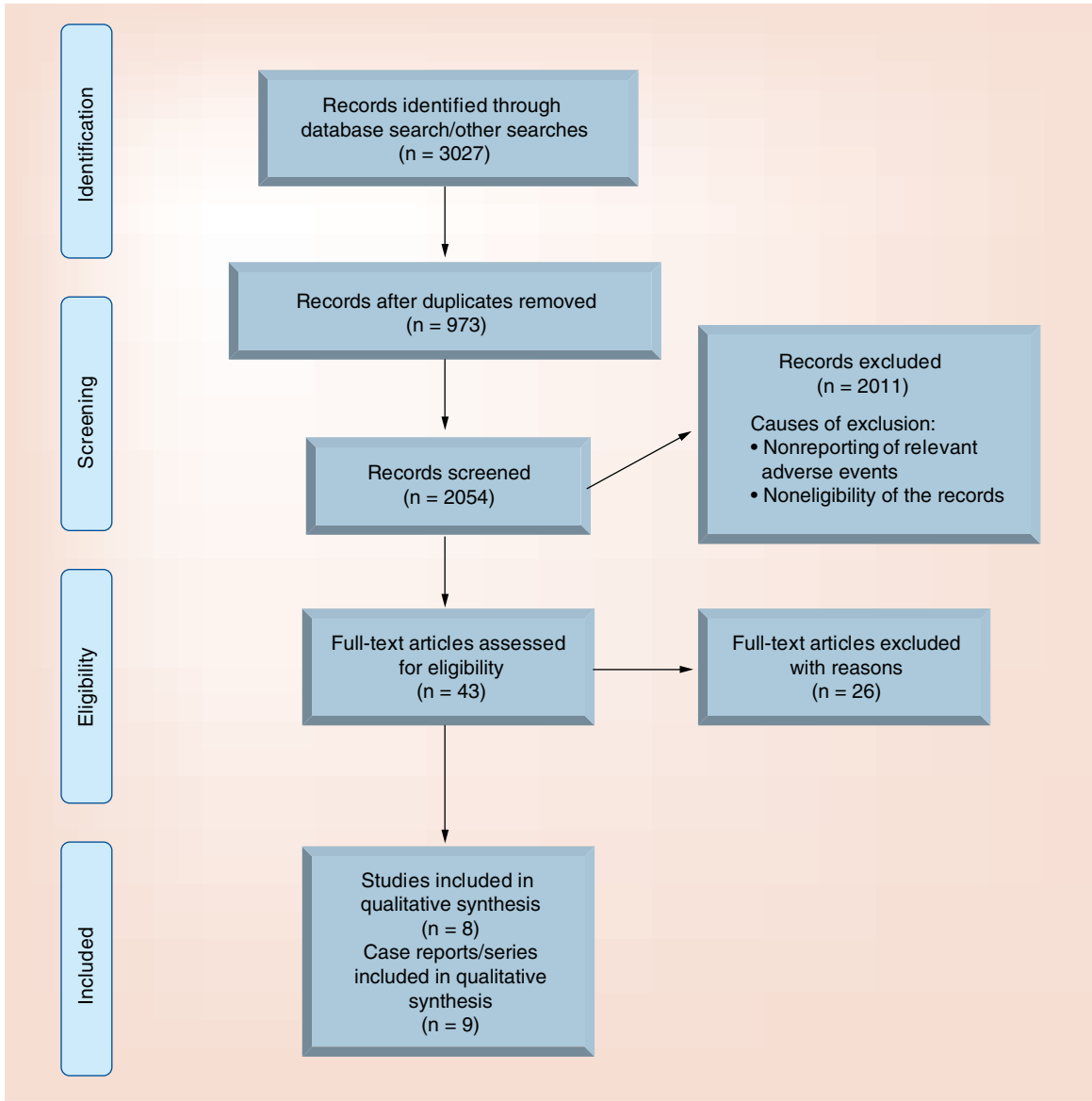

Figure 1. Flowchart of study selection procedure.

- Pembrolizumab: two Phase II studies (one in advanced urothelial cancer including 33 patients, and the second one in advanced melanoma including 173 patients); and three Phase III studies (one in advanced urothelial cancer including 542 patients and two in advanced NSCLC including 1339).
- No eligible atezolizumab studies were found reporting musculoskeletal adverse events.

Pattern of reported neurological toxicities in the clinical trials

Among the eight included studies, arthritis was reported in three studies and myositis was reported in five studies. The incidence of arthritis ranged from 1 to 22%; while the incidence of myositis ranged from 0.4 to 6%. There were no sufficient details to describe discontinuation of ICIs because of arthritis or how many patients had persisting arthritis after stopping the ICIs.

Included case series/reports

Nine case reports/series describing the musculoskeletal events of 12 patients (Table 2) (including 7 male and 5

Table 2. Selected case reports reporting the details of potentially immune-related musculoskeletal toxicities with immune checkpoint inhibitors.

Case report	Patient characteristics	Pattern of musculoskeletal events	Time course of the event	Treatment
Pembrolizumab-associated events				
Haddox *et al.* (2017)	A 78-year-old man with BRAF wild-type metastatic melanoma with predominantly osseous metastases	Immune-mediatednecrotizing myopathy of the diaphragm	2 weeks after the second cycle ofpembrolizumab	Prednisone was initiated at 1 mg/kg, a week after he experienced worsening bulbar myopathy and respiratory weakness. He was initiated on plasma exchange (PLEX) but with no improvement so he was intubated
Vallet *et al.* (2016)	An 86-year-old woman, with stage IIa, Breslow 3 mm, Clark level IV, acrolentiginous melanoma of the right index	Necrotic myositis. Electroneuromyography showed myopathic changes without abnormalities on repetitive stimulation. Muscle biopsy showed multifocal necrosis with adjacent endomysial $CD8^+$ T-cell predominant infiltrates, without inclusion bodies	4 days after the second injection of pembrolizumab (2 mg/kg every 3 weeks)	Pembrolizumab was discontinued and treatment with intravenous corticosteroids was commenced (1 gram per day). At day 3, her axial and limbs weakness improved by >50% and creatine phosphokinase (CPK) levels normalized
Zimmer *et al.* (2016)	A 79-year-old male with metastatic melanoma	Grade 3 myositis	1 week after initiation of pembrolizumab	Prednisolone 1 mg/kg/day; forced diuresis; pause of pembrolizumab. The myositis improved with treatment
	A 77-year-old male with metastatic melanoma	Grade 4 myositis	7 weeks after initiation of pembrolizumab	Prednisolone 2 mg/kg/day; analgesic therapy. Patient improved with treatment
	A 54-year-old male with metastatic melanoma	Grade 3 myositis	1 week after initiation of pembrolizumab	Patient refused treatment with spontaneous improvement
	An 81-year-old female with metastatic melanoma	Grade 1 myositis	6 weeks after initiation of pembrolizumab	It resolved with corticosteroids 1 mg/kg/day
Nivolumab-associated events				
Saini *et al.* (2017)	A 35-year-old male with stage IIA classical Hodgkin lymphoma, received nivolumab 3 mg/kg biweekly	Myositis and the patient complained of left upper arm pain and was found to have a 1–2 cm area of induration	After the ninth cycle of nivolumab	Prednisone 100 mg once daily for 5 days with a rapid taper. Within 48 h of completing his prednisone taper his condition again worsened. He was again initiated on prednisone with prompt resolution
Gauci *et al.* (2017)	An 80-year-old man with a superficial spreading melanoma received first-line treatment with nivolumab (3 mg/kg/2 weeks)	Patient presented with symmetric inflammatory arthralgia and synovitis of distal joints affecting the proximal interphalangeal joints, wrists and ankles, and synovitis of the proximal interphalangeal joints and wrist, associated with edema on both hands and forearms	At week 4, before the 3rd nivolumab infusion	Nivolumab treatment was suspended. Corticosteroids were started at 0.3 mg/kg/day for 2 weeks, but response was insufficient. The inflammation resolved after increasing the dose to 0.5 mg/kg/day
Fox *et al.* (2016)	A 75-year-old female with recurrent invasive melanoma which was re-excised, nivolumab was started at 3 mg/kg every 2 weeks	Proximal muscle myopathy	After second dose of nivolumab	Nivolumab was discontinued, and the patient was started on prednisone. After these interventions, the patient's symptoms subsided, and the CPK normalized after 8 days
Yoshioka *et al.* (2015)	An 84-year-old man with history of excised malignant melanoma, receiving nivolumab for residual metastases	Myositis with respiratory compromise	7 weeks after starting nivolumab	Discontinuation of the offending agent resulted in clinical improvement and normalization of muscle enzymes
Ipilimumab-associated events				
Yamaguchi Y *et al.* (2016)	A 70-year-old Japanese woman with lung carcinoma received three courses of two courses of carboplatin and etoposide therapy, and the evaluation after these two courses revealed a partial response. Therefore, ipilimumab was added to the third course	Dermatomyositis (skin rash and myositis)	23 days after the start of the third course	Oral prednisolone at 60 mg daily (1 mg/kg/day) was started and ipilimumab discontinued. Clinical improvement was achieved in 2 weeks
Sheik *et al.* (2015)	A 50-year-old woman with stage IVB-RAFV600E mutant malignant melanoma with metastases of the liver, lungs, and peritoneum. She was started on a course of ipilimumab, 3 mg/kg, intravenously every 4 weeks	Dermatomyositis (she developed an erythematous and pruritic eruption plus muscle weakness)	Within 2 weeks of the first dose	Patient was treated with prednisone at an initial dose of 60 mg/day with tapering over 4 weeks with partial resolution of the eruption. Ipilimumab was withheld

NSCLC: Non-small-cell lung cancer.

female patients) who developed arthritis, myositis and/or myopathy while they were on or shortly after receiving ICIs.

Their age ranged from 35 to 86 years. Among the 12 patients, ten were treated for malignant melanoma; one patient was treated for NSCLC and another one for Hodgkin lymohoma. Six patients were on pembrolizumab, four patients were on nivolumab and two patients were on ipilimumab.

Eleven patients developed myositis/inflammatory myopathy while only one patient developed arthritis. Among the patients with myositis, two patients had dermatomyositis.

The time of onset varied from 1 week from the start of an ICI to >18 weeks after the start of an ICI. The signs and symptoms improved with only discontinuation of the ICI in two patients. In the other ten patients, management necessitated adding steroids and/or other immunosuppressives with clinical improvement in all cases except one case.

Discussion

Musculoskeletal involvement is a traditional hallmark of many autoimmune conditions. Given the fact that ICIs traditionally induce widespread autoimmune reaction, it is not surprising to have some musculoskeletal adverse events as part of the spectrum of ICIs-associated toxicities. The most commonly reported musculoskeletal adverse events with many ICIs were arthralgia and/or myalgia. However (and as clarified in the methods section of this review), it is difficult to prove the immune-related etiology of either arthralgia or myalgia among cancer patients (because of the significant probability of being caused by factors other than ICIs). Thus, the current analysis is focused on arthritis and myositis because of their straightforward autoimmune nature.

Although the overall incidence of immune-related musculoskeletal toxicities is rare in the current review, it is crudely noted in our results that musculoskeletal toxicities may be more probable with PD-1 inhibitors compared with CTLA-4 inhibitors. This observation is consistent with previous reports [50]; and it suggests that further research into the pathogenesis of musculoskeletal toxicities is warranted.

Most of the published recommendations regarding side effects of ICIs tackle the more common IRAEs (e.g., gastrointestinal, endocrine or cutaneous toxicities) with little mention of the rheumatologic toxicities [51]. Recently, the European Society of Medical Oncology published a dedicated guideline for the management of immunotherapy toxicities; and fortunately it discussed rheumatologic toxicities within it [52]. The European Society of Medical Oncology guideline suggested that for mild to moderate symptoms, mild analgesia with paracetamol or NSAIDs may be enough. Low-dose steroids may be additionally considered for moderate symptoms; while high-dose steroids and/or other steroid-sparing drugs may be needed for severe symptoms. Additionally, the current review suggests that temporary dose interruption may help in the control of some rheumatologic symptoms. This management strategy is consistent with that proposed for more common IRAEs [43]. Rarely, some cancers may induce the development of autoimmune rheumatologic manifestations (e.g., dermatomyositis with lung cancer) as a paraneoplastic syndrome [53]. From a clinical perspective, it may be impossible sometimes to differentiate whether the autoimmune myositis or arthritis is caused by the drug or the tumor itself. Thus, consultation with a specialist rheumatologist should be considered with severe cases or complex clinical scenarios.

A history of an autoimmune disorder was usually regarded as an exclusion criterion for many of the trials evaluating ICIs. Thus, it remains to be known if the use of ICIs would exacerbate musculoskeletal manifestations of other autoimmune diseases (e.g., rheumatoid arthritis or systemic lupus erythematosus) [54].

IRAEs were hypothesized to work as a surrogate marker of response to ICIs in some cases [55]. However given the rarity of the musculoskeletal adverse events' data, it is almost impossible to conclude about the relationship between musculoskeletal toxicities and response to ICIs treatment.

Given the heterogeneity of the included reports in terms of diseases treated, agents administered and design of the studies, the results of this review have to be carefully approached. This is coupled with the retrospective nature of the case reports included in the review which further weakens the level of evidence. Likewise, the absence of data about concomitant medications and concurrent medical conditions further confounds the results of this review.

Conclusion

Immune-related arthritis and myositis occur uncommonly in cancer patients treated with ICIs. Further studies are required to better describe the pathogenesis as well as the time course of these events. Multidisciplinary approach is warranted in the management of IRAEs.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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