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Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature

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Abstract

Background—Immune checkpoint inhibitors (ICI) are improving prognosis in advanced stage cancers, but also lead to immune-related adverse events (IRAE). IRAEs targeting many organ systems have been reported, but musculoskeletal and rheumatic IRAE have not been well characterized. We systematically reviewed published literature on musculoskeletal and rheumatic IRAE to better understand prevalence and clinical characteristics.

Methods—Medline and CENTRAL databases were searched for articles reporting rheumatic and musculoskeletal IRAEs secondary to ICI treatment. After screening abstracts and full texts in duplicate, clinical features, prevalence and treatment data were extracted and summarized.

Results—1725 unique abstracts were screened; 231 contained original data and were about ICIs and went to full text screening. Fifty-two of these contained information about musculoskeletal or rheumatic IRAEs or about treatment with ICIs in pre-existing autoimmune disease. Of these, 33 were clinical trials, 3 were observational studies, and 16 were case reports or series. Arthralgia prevalence in clinical trials ranged from 1–43%, and myalgia was reported in 2–20%. Arthritis was reported in 5/33 clinical trials, and vasculitis was reported in only 2. One observational study and 3 case reports described patients with pre-existing autoimmune disease treated with ICIs. Case reports included development of inflammatory arthritis, vasculitis, myositis, and lupus nephritis.

Conclusions—Arthralgia and myalgia have been reported commonly in patients treated with ICIs. The prevalence of rheumatic IRAEs like inflammatory arthritis, vasculitis, and sicca syndrome is less clear from current evidence. There is limited observational and case-level evidence describing ICI use in patients with pre-existing autoimmune disease.

Understanding of the complex relationships between autoimmunity and malignancy continues to evolve. Observations of concurrent or tightly temporally associated autoimmune disease and cancer date back to the early 1900s when cases of myositis associated with gastric and breast cancers were described. Since then, data have emerged suggesting that naturally occurring anti-tumor immune responses may trigger the

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development of autoimmunity in diseases such as scleroderma and myositis. For instance, scleroderma patients with RNA polymerase III antibodies have an increased risk of cancer around the time of scleroderma onset,[12] and mechanistic studies suggest that mutations of autoantigens in cancers may trigger immune responses that become cross-reactive in these patients[3]. In myositis, the myositis-specific antibodies TIF-1 gamma[45] and NXP-2[56] have been associated with a significantly higher risk of cancer-associated myositis.

In addition to naturally occurring anti-cancer immune responses triggering autoimmunity, it is increasingly recognized that therapies for cancer can trigger similar responses. Immune checkpoint inhibitors (ICIs) 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. When CTLA-4 and PD-1 engage with their ligands on antigen presenting cells, B7 for CTLA-4 and PD-L1 or PD-L2 for PD-1, T-cell activation is inhibited. Tumors can also express inhibitory ligands like PD-L1 on their cell surfaces, thus downregulating the T-cell response. ICIs block these negative interactions between T-cells, antigen presenting cells and tumors, allowing positive costimulation to occur and T-cells to become activated. Many clinical trials with drugs targeting these and other related immune pathways, including T-cell immunoglobulin and mucin domain-3 (TIM-3), CD137, V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA), and lymphocyte activation gene-3 (LAG-3), are underway for a wide variety of indications[78].

These immune checkpoints are also relevant in the pathogenesis and treatment of rheumatic diseases[8]. In cancer therapy, ICIs block negative costimulation; whereas, in the treatment of autoimmunity, negative costimulation is promoted. For example, abatacept, a fusion protein of the extracellular domain of CTLA-4 and the Fc portion of IgG1, is an effective treatment for rheumatoid arthritis. This drug works by blocking binding of the positive costimulatory molecule CD28 to its receptor, CD80/86. Drugs targeting other immune checkpoints are also being investigated to treat autoimmunity.

ICIs have been paradigm shifting in the treatment of advanced malignancies and are currently approved for multiple indications: metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), bladder cancer, head and neck cancer, and Hodgkin’s lymphoma. Ipilimumab, targeting CTLA-4, was the first ICI approved for metastatic melanoma. Ipilimumab has shown survival benefit when compared to chemotherapy[9] or peptide vaccine[10] controls in phase 3 trials for melanoma. Nivolumab, targeting PD-1, is approved for metastatic NSCLC, RCC, and Hodgkin’s lymphoma in addition to metastatic melanoma, with significant survival benefits when compared to conventional chemotherapy[11–13]. Pembrolizumab, also targeting PD-1, has shown 26 to 31% response rates in patients with metastatic melanoma refractory to Ipilimumab[14]. Pembrolizumab is also approved for a subset of lung cancer and metastatic head and neck cancer. Atezolizumab, a PD-L1 inhibitor, is approved for urothelial carcinoma with data showing better tolerance and increased response when compared to traditional treatments[15].

ICIs are now being used in combination with even better response rates. For example, a 60% response rate was seen using Nivolumab and Ipilimumab for metastatic melanoma, as compared to an 11% response rate for Ipilimumab alone[16].

Although these therapies have been effective, there are significant consequences as a result of activation of the immune system leading to tissue damage, or immune-related adverse events (IRAEs). IRAEs have affected nearly every organ system and range widely in severity. While colitis, hepatitis, pneumonitis and other IRAEs are well documented, IRAEs with rheumatic and musculoskeletal phenotypes are less well described. Events like inflammatory arthritis, arthralgia, myositis, and sicca syndrome induced by ICIs are increasingly being appreciated. In this study, we aimed to review the literature about IRAE with rheumatic and musculoskeletal manifestations as these are events most likely to be referred to rheumatology. We also examined the use of ICIs in those with pre-existing autoimmune conditions.

METHODS

A systematic review of published literature reporting IRAEs secondary to inhibition of PD-1, CTLA-4 or PD-L1 was performed.

Identification of studies

Two search strategies were utilized. A literature search of Medline was performed with a search string that combined the concepts of immune checkpoint inhibitors and their targets with manifestations of immune mediated or inflammatory adverse events. The names of approved drugs at the time of the search, ipilimumab, nivolumab, pembrolizumab and the targets of drugs, PD-1, PD-L1 and CTLA-4 were included. Rheumatic and musculoskeletal manifestations and select other IRAEs were also queried encompassing the terms arthralgia, arthritis, synovitis, xerostomia, xerophthalmia, sicca, Sjogren's syndrome, SLE, myositis, vasculiitis, colitis, thyroiditis, hypophysitis, endocrinopathy, pneumonitis, vitiligo and hepatitis. The full search string is detailed in Supplement 1.

An additional search for clinical trials in the Cochrane database using the targets of ICIs (PD-1, PD-L1, CTLA-4), the names of approved ICIs at the time of the search (ipilimumab, nivolumab, pembrolizumab), and the clinical trials filter was also performed. Results published prior to February 8th, 2016 were included. Results were de-duplicated with computer software and checked manually.

Screening process

The abstracts were screened for relevance to the topic and inclusion of original data. Abstracts were screened in duplicate (LCC and AKG) and any discrepancies were resolved with discussion. Any results not related to ICIs and IRAEs or not containing original data (e.g. reviews, meta-analyses, letters to the editor) were excluded. References of the meta-analyses were evaluated for studies potentially missed by the two searches.

Full text screening evaluated articles for mention of arthritis, arthralgia, back pain, joint pain, musculoskeletal pain, myositis, myalgia, muscle weakness, vasculitis, polymyalgia

rheumatica, Sjogren's syndrome, sicca syndrome, dry mouth, dry eyes, systemic lupus erythematosus, or other connective tissues diseases as a result of ICIs. This process also evaluated for treatment with ICIs in the context of pre-existing autoimmunity. Full text screening was also performed in duplicate.

Data extraction

Studies were grouped by type of study: case series or reports, observational studies, and clinical trials. For clinical trials, the indication, drug/s studied, dosing regimen and incidence of above events were recorded. For observational studies, the indication for treatment, drug/s used, the type of study (prospective, retrospective, case-control), clinical features of IRAE, and information on underlying autoimmune disease were extracted. For case reports and series, clinical features of the IRAE described including symptoms, examination, laboratory studies, imaging and treatment received were extracted in addition to the type of cancer and type of ICI used and any information on pre-existing autoimmune disease.

Quality assessment

Since the outcome of interest was adverse events, bias related to ascertainment of these events was assessed for the included clinical trials. Categories assessed were sequence generation, allocation concealment, blinding of adverse event assessment, incomplete adverse event data, and selective adverse event reporting using the Cochrane Collaboration's tool[17]. The observational studies and case reports were not evaluated with this tool as none were prospective studies, and thus the Cochrane tool did not apply[17]. Factors potentially contributing to risk of bias in these studies including size and consideration of confounders are discussed in the Results section.

RESULTS

The two searches yielded 1725 unique results after de-duplication (Figure 1). There were 231 abstracts about IRAE that contained original data, which went on to full text screening. Of these full text articles, 52 mentioned a musculoskeletal or rheumatic manifestation of IRAE and were included in the qualitative synthesis. Thirty-three were clinical trials, three were observational studies, and 16 were case series or reports.

The majority of studies were from the United States (N=26, 50%), with France, the Netherlands, Japan, the United Kingdom, Germany, Canada, and Australia also represented. Thirteen of the clinical trials had sites in multiple nations. ICIs administered included ipilimumab (anti-CTLA4), nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), tremelimumab (anti-CTLA4), and one anti-PDL-1 antibody (MDX-1105).

Clinical trials

The 33 clinical trials (full references in Supplement 2) were heterogeneous in a variety of features. There were phase 1 through 3 trials included (Table 1). Some trials combined ICIs with other therapies, including chemotherapy, vaccines, and granulocyte colony stimulating factor (G-CSF). Several trials included only grade 3 or higher adverse events in the report rather than all events (e.g. Hodi JAMA 2014); therefore, many musculoskeletal and

rheumatic events may not have been captured. In the grading system used for adverse events in oncology clinical trials, grade 3 events are defined as disabling, requiring prolonged hospitalization, or limiting self-care activities of daily living. Grade 4 events are those that are life threatening and require urgent intervention. The diseases treated were also wide-ranging. Some trials focused on one disease like metastatic melanoma, and others included any advanced solid tumors. The outcomes of interest, IRAEs, were not recorded in a consistent manner throughout the trials. Different trials reported different IRAEs, and no trial reported all IRAEs of interest. Due to the heterogeneity in interventions and ascertainment of adverse events, no meta-analysis for combined incidence estimates was performed.

Arthralgia was most commonly reported (N=24 trials) musculoskeletal or rheumatic IRAE in clinical trials, with development of arthralgia in 1–43% of participants exposed to ICIs. Arthritis was reported in only five trials with a range of 1–7%. Myalgia was second most commonly reported (N=12 trials) and was present in 2–21% of trial participants. Dry eyes and dry mouth were reported in three and four trials respectively and incidence ranged from 3–24%. Two trials reported vasculitis: giant cell arteritis in one, and no further specification of vasculitis in the other. Additional events of interest reported in a limited number of trials were sarcoidosis, autoimmune disease, back pain, bone pain and musculoskeletal pain (Table 1).

Observational studies

Only three observational studies were included in the present review. One study was a review of radiology on 119 patients treated with CTLA-4 inhibition[18]. CT scans and PET scans were evaluated, with arthritis noted by imaging in 3.4%. None of these patients were RF or CCP positive. A second observational study reviewed the clinical features of a series of 198 patients treated with ipilimumab plus or minus vaccines for melanoma or RCC.[19] In in this report, 2% developed grade 3 or 4 arthritis. Lower grade events were not reported. A third observational study reported on 30 patients treated with ipilimumab who had pre-existing autoimmune disease[20], in which 8 patients had an exacerbation of their autoimmune disease and 10 developed another IRAE after treatment with ipilimumab.

Case series and reports

There were 16 case series and reports of patients developing rheumatic phenotypes after treatment with ICIs or of patients with known autoimmune conditions treated with ICIs. The clinical features and treatment of included cases are described in Table 2.

Inflammatory arthritis/arthropathy—Two cases of inflammatory polyarthritis and tenosynovitis were reported after treatment with pembrolizumab for metastatic melanoma[21]. Both patients were negative for ANA, RF, and anti-CCP antibodies. Another case report described reducible swan neck deformities in the hands that developed along with uveitis after treatment with nivolumab[22].

Inflammatory myopathy/eosinophilic fasciitis—Myositis similar to dermatomyositis (one case)[23] and polymyositis (two cases)[24][25] was described in three separate case reports.

Ipilimumab was the inciting agent for the case of dermatomyositis and one of the cases of polymyositis; nivolumab use preceded the development of the other case of polymyositis. All three patients improved with corticosteroids (Table 2). Another patient who presented with myalgias was ultimately found to have eosinophilic fasciitis[26].

Vasculitis—Vasculitis has been reported in single organs and in the form of giant cell arteritis. Single organ vasculitis in the retina[27] and uterus[28] has also been reported, though the case in the retina was not definitively due to pembrolizumab and may have been a paraneoplastic process given the ocular melanoma in this patient. Giant cell arteritis and polymyalgia rheumatica were reported in two patients treated with ipilimumab for metastatic melanoma, with successful treatment using prednisone monotherapy[29].

Lupus nephritis—One case report of lupus nephritis after treatment with ipilimumab was included[30]. The patient had a renal biopsy showing extramembranous and mesangial deposits of IgG, IgM, C3, C1q, and positive antibodies to double stranded DNA. The dsDNA antibodies resolved after treatment with corticosteroids.

Pre-existing autoimmune disease and ICI treatment—Three cases described inflammatory bowel disease (Crohn's disease or ulcerative colitis) in patients treated with ipilimumab for metastatic melanoma. Two patients did well with no major flare of their inflammatory bowel disease[3132]. The third case report by Bostwick described a patient who had a severe flare of ulcerative colitis while on treatment, requiring an urgent colectomy[33]. Another case reported was the development of acute interstitial nephritis in a patient with pre-existing Sjogren's syndrome after ipilimumab therapy[34].

Others—Orbital myositis[35] and encephalopathy with arthralgias[36] were also described in case reports as shown in Table 2.

Quality of included studies

For clinical trials, quality assessment is summarized in Table 3. Most of the clinical trials were not blinded in terms of outcome assessment of adverse events, contributing to potential bias in the results. Many were not randomized. Many of the trials had a small sample size, and thus may not be representative of larger populations treated with ICIs, introducing some bias. Since many of the studies were earlier clinical phases, safety, including the development of adverse events, was a main focus so incomplete data was less of an issue. Selective event reporting was present in several studies where only frequent or high grade adverse events were reported.

The observational studies were all retrospective in their scope. No studies took into account potentially confounding variables. Two studies had sample sizes greater than 100, while the other had a sample size of only 30 patients. As has been noted, case series and reports represent lower quality evidence, with an inherent risk of reporting bias since only events of interest are described. Nonetheless, when describing a new entity in terms of its clinical manifestations, such spontaneous reports provide important information to describe the range of phenotypes possible as for ICI-induced autoimmune and musculoskeletal manifestations.

DISCUSSION

Several important findings were noted in this first review of rheumatic and musculoskeletal IRAE due to ICIs. We aimed to evaluate the prevalence of these types of IRAEs, their clinical characteristics and treatments to help guide rheumatologists and oncologists in their evaluation of these patients. Rates of arthralgia were most commonly reported in clinical trials and ranged widely, from 1 to 43%. Other musculoskeletal and rheumatologic adverse events were less commonly reported. Case series and reports illustrated a wide variety of rheumatic phenotypes seen after treatment with ICIs, including inflammatory arthritis, inflammatory myopathy, vasculitis, and lupus nephritis. The success and safety of treating those with known autoimmune disease with ICIs varied in the included case reports and observational study. Some patients had flares of their autoimmune disease and/or developed other IRAEs from ICI treatment, while others tolerated ICIs without incident.

This study was unique in being the first to focus on musculoskeletal and rheumatic IRAE as a consequence of treatment with ICIs. Other systematic reviews have focused on case reports of all types of IRAEs[37] or IRAEs due to CTLA-4[38] inhibition, but no study to our knowledge has reviewed the published literature with the same focus as this review. It is also the first to synthesize information from different studies on treating patients with known autoimmune disease with ICIs. The descriptions of the variety of clinical presentations can help oncologists and rheumatologists in recognizing potential IRAEs. Areas for future study were identified by the lack of information found on epidemiology, treatment and evaluation of rheumatic and musculoskeletal IRAEs, and using ICIs in patients with autoimmune disease.

To put our findings in context, the incidence and clinical characteristics of IRAEs with other phenotypes range widely. Colitis and hepatitis, associated with potential mortality, have been reported in up to 2% of patients treated with ICIs[3940]. Other IRAEs are more common but less severe. Inflammatory skin conditions, like vitiligo and other rashes, are seen in up to 30% of those treated[14], and thyroid dysfunction occurs in as many as 22% of patients treated[41]. IRAEs affecting the peripheral and central nervous system, kidneys, pancreas and eyes have also been described[42]. The prevalence of IRAEs differ by type of therapy and indication for treatment. Pneumonitis is more common in those treated with nivolumab for NSCLC and RCC[1112] (4–5%) as compared to melanoma[43] (1.5%). Colitis has been reported more commonly from ipilimumab than nivolumab in melanoma, with rates of about 5%[10] compared to 1%[4445] respectively. Combination therapy with both ipilimumab and nivolumab has shown the highest rates of colitis[46]. The time course for IRAEs also differ, with rash and colitis developing early, and pneumonitis and endocrinopathies occurring later[47].

In this review, we were not able to comment on the time course for developing musculoskeletal and rheumatic IRAEs, nor the association between particular drugs or tumors and specific events, due to lack of information in the published literature. The lack of complete reporting of the events of interest in the included clinical trials made it difficult to see which drugs were associated with particular rheumatic or musculoskeletal IRAEs. Only two clinical trials included in this report used combination therapy, so it is also unclear if combination therapy will lead to higher rates of events. The association of specific adverse

events with particular drug regimens is an important area for investigation. In our limited experience, we have seen persistence of rheumatic IRAEs beyond the cessation of ICI therapy[48], which, if confirmed in future studies, has significant implications on the long-term management of these patients.

Since our initial search, several relevant articles have been published. Our group has reported the largest case series of inflammatory arthritis and sicca syndrome secondary to ICIs[48]. In this series, patients with ICI-induced inflammatory arthritis were seronegative for traditional antibodies associated with rheumatoid arthritis. They required higher doses of steroids for their inflammatory arthritis, and some required additional immunosuppression with methotrexate or TNF-inhibitors. Concomitant colitis, thyroiditis, acute interstitial nephritis, or pneumonitis were present in a subset of patients.

Also after our search was conducted, a case series of 13 patients who had renal biopsies after developing acute kidney injury while being treated with immunotherapy[49] was published. Several patients had coexisting IRAEs. One patient treated with nivolumab also had concomitant sicca syndrome with tubulointerstitial nephritis that was lymphocyte predominant on renal biopsy, similar to a patient described in our case series of ICI-induced sicca syndrome[48]. Both this study and our own study suggests that developing one IRAE is a risk factor for developing musculoskeletal and rheumatic IRAEs.

A limitation of this review is the lack of clinical information on IRAEs provided from clinical trial manuscripts. The classification of the events was likely inconsistent among studies. For example, in a 2010 trial of nivolumab for refractory solid tumors[50], two patients were classified as having “arthralgia” but required corticosteroid treatment. It is possible that they actually had inflammatory arthritis rather than just joint pain. The inclusion of only high grade events (grades 3 or higher) in some trials also limited the information on musculoskeletal and rheumatic events that could be extracted from the clinical trial manuscripts. Oncology and rheumatology grading systems for adverse events differ, and musculoskeletal events with substantial functional impact (e.g. limiting instrumental activities of daily living) may be only a grade 2 event by the Common Terminology Criteria for Adverse Events (CTCAE) system used by oncology;[51] whereas, they would be a grade 3 event in the Rheumatology Common Toxicity Criteria (RCTC) sytem.

Additionally, our search did not include therapies outside of those targeting PD-1, CTLA-4 and PD-L1 as we wanted to focus on approved targets for therapies at the time. Many other related pathways are being targeted in clinical trials of novel agents, but data is more preliminary for these targets.

In summary, a variety of rheumatic and musculoskeletal IRAE have been described after treatment with ICIs. Rates of arthralgia and myalgia have been widely reported, but other IRAE like arthritis and vasculitis are not consistently described. The case reports highlighted in this review illustrate the wide variety of rheumatic IRAE that rheumatologists are likely to encounter as ICI use expands. Future research should focus on knowledge deficits in epidemiology, evaluation, and treatment of rheumatic and musculoskeletal IRAE. Better

understanding of why these musculoskeletal IRAE develop and how to treat them will benefit patients and could give insight into pathogenesis of traditional rheumatic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovation

- Arthralgia and myalgia were commonly reported in trials of immune checkpoint inhibitors.
- There are no estimates for prevalence or incidence of rheumatic immune-related adverse events in the current literature.
- Case reports highlight a diverse group of rheumatic manifestations after treatment with immune checkpoint inhibitors that may be referred to rheumatologists.
- Immune checkpoint inhibitors have been used in those with pre-existing autoimmune disease and can precipitate flare of the autoimmune disease in some patients.

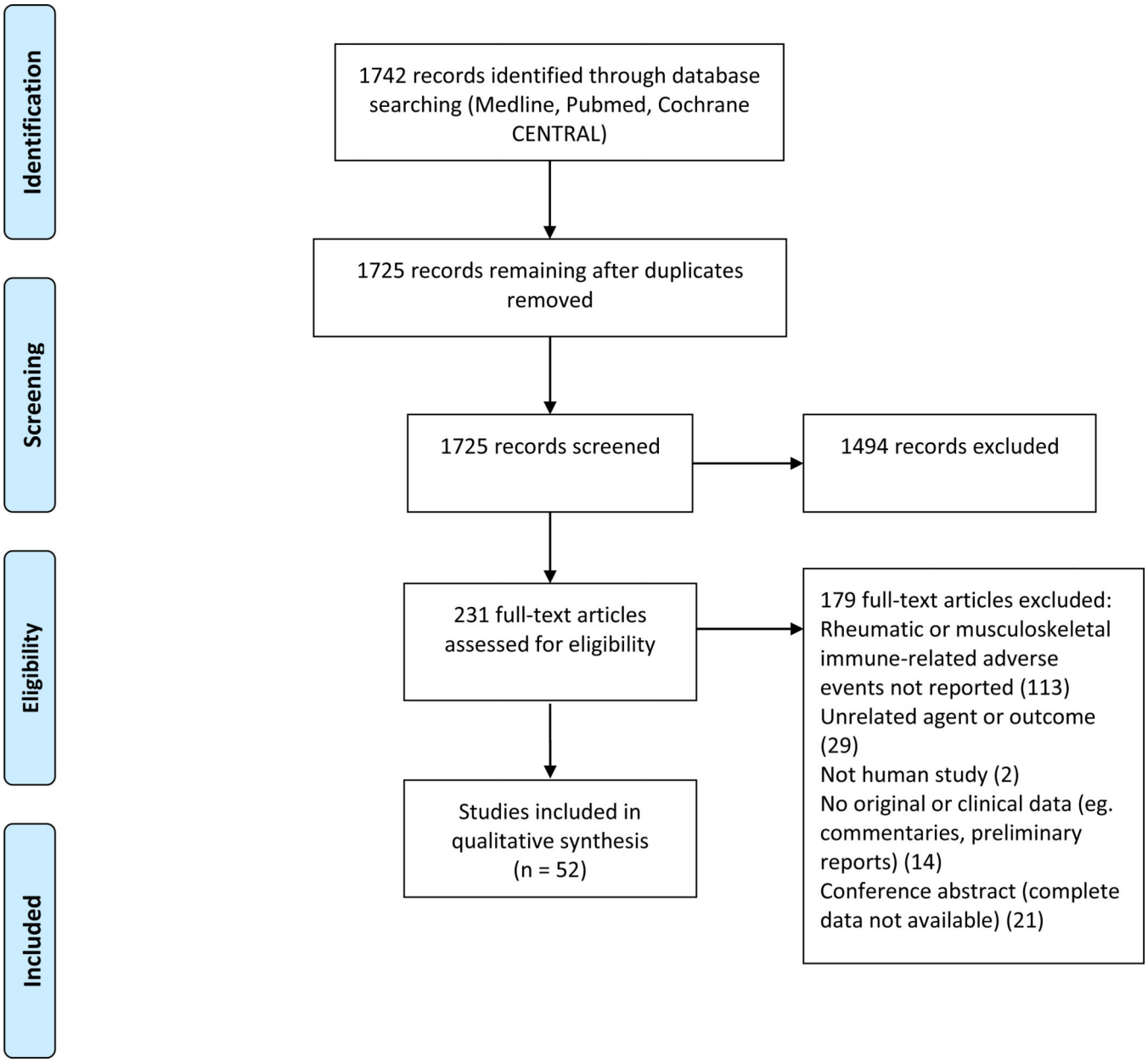

Figure 1.
PRISMA flow chart of studies included

Table 1

Characteristics of clinical trials and incidence of reported musculoskeletal and rheumatic IRAE.

Author, year	Trial phase	Indication	Number exposed	Drug/s	Dose	Arthralgia	Arthritis	Dry eyes	Dry mouth	Myalgia	Muscle weakness	Vasculitis	Other
Anti-CTLA-4													
Bashey 2009	1	Relapse after hematopoetic stem cell transplant	29	Ipilimumab	Dose escalation	NR	2 (7%)	NR	NR	NR	NR	NR	“bone pain”: 1 (3%); “muscle cramps”: 1 (3%)
Downey 2007	2	Metasatic melanoma	139	Ipilimumab (+/− peptide vaccine)	3 mg/kg in one group, dose escalation in other	10/73 (13.7%) with peptide; 4/66 (without peptide	NR	NR	NR	NR	NR	NR	NR
Hersh 2014	2	Advanced melanoma	72	Ipilimumab +/− dacarbazine	3 mg/kg	NR	NR	NR	NR	NR	NR	1/35 (3%) in ipi + dacarbazine	NR
Hodi 2014 (1) Cancer Immunol Res	1	Metasatic melanoma	46	Ipilimumab +/− bevacizumab	3 mg/kg or 10 mg/kg	13 (28%) “joint pain”	NR	2 (4%)	NR	6 (13%) “muscle pain”	NR	1 (2%) with GCA	“joint function” problems: 1 (2%)
Hodi 2014 (2) JAMA *	2	Metasatic melanoma	245	Ipilimumab +/− sargramostim	10 mg/kg	3/118 (3%) in combination; 1/120 (1%) in ipi alone	1/118 (1%) in combination	NR	NR	2/118 (2%) combination; 4/120 (3%) ipi alone	1/118 (1%) combination; 1/120 (1%) ipi alone	NR	“autoimmune disease”: 4/120 (3%) in Ipi alone
Kwon 2014	3	Metastatic prostate cancer	399	Ipilimumab + radiation	10 mg/kg	44/393 (11%)	NR	NR	NR	NR	NR	NR	MSK pain: 32 (8%)
Le 2013	1	Pancreatic cancer	30	Ipilimumab +/− GVAX	10 mg/kg	Ipi + GVAX: 1/15 (75)	NR	Ipi: 1/15 (7%)	NR	NR	NR	NR	NR
Lynch 2012	3	NSCLC	138	Ipilimumab + carboplatin, paclitaxel (concurrent or phased)	10 mg/kg	Concurrent: 16/71, (22.5%) phased: 12/67 (18%)	NR	NR	NR	NR	NR	NR	NR
Merchant 2015	1	Advanced solid tumors (pediatric)	33	Ipilimumab	Dose escalation	NR	NR	NR	NR	1/33 (3%)	NR	NR	NR
Prieto 2012 *	1/2	Metastatic melanoma	177	Ipi + peptide vaccine; Ipi + IL-2, Ipi dose escalation +	various	NR	1/36 (3%) in Ipi + IL-2; 1/85 (1%) in Ipi DE + peptide	NR	NR	NR	NR	NR	NR

Author, year	Trial phase	Indication	Number exposed	Drug/s	Dose	Arthralgia	Arthritis	Dry eyes	Dry mouth	Myalgia	Muscle weakness	Vasculitis	Other
				peptide vaccine			vaccine						
Reck 2013	2	Extensive disease small cell lung CA	85	Ipilimumab + chemotherapy, concurrent or phased	10 mg/kg	24% in concurrent; 46% in phased	NR	NR	NR	NR	NR	NR	NR
Robert 2011		Metastatic melanoma	247	Ipilimumab + dacarbazine	NR	NR	NR	NR	NR	NR	NR	NR	Back pain 28/247 (11.3%)
Sarnaik 2010	2	Stage III/IV melanoma	75	Ipilimumab + peptide vaccine	3 mg/kg, 10 mg/kg	Arthritis/arthralgia 17/75 (23%)		2/75 (3%)	NR	Myositis/ myalgia 16/75 (21%)	NR	NR	NR
Weber 2008 *	1/2	Metastatic melanoma	88	Ipilimumab	Various	1/88 (1%)	NR	NR	NR	NR	NR	NR	Pain in extremity: 1/88 (1%)
Yamazaki 2015	2	Previously untreated advanced melanoma	15	Ipilimumab + dacarbazine	10 mg/kg	NR	NR	NR	NR	NR	NR	NR	Back pain: 4/15 (27%)
Yang 2007	2	Metastatic RCC	47	Ipilimumab	Various	1/47 (2%)	NR	NR	NR	NR	NR	NR	NR
Calabro 2014	2	Malignant mesothelioma	29	Tremelimumab	Dose escalation	4 (14%)	NR	NR	NR	NR	NR	NR	NR
Ralph 2010	2	Advanced gastric and esophageal adenocarcinoma	18	Tremelimumab	15 mg/kg	3/18 (17%)	NR	NR	NR	NR	NR	NR	NR
Sangro 2013	2	HCC and hepatitis C	21	Tremelimumab	15 mg/kg	NR	1/21 (5%)	NR	NR	NR	NR	NR	NR
Anti-CTLA-4 vs. Anti-PD-1													
Robert 2015 (2) Pembro	3	Advanced melanoma	811	Ipilimumab vs. Pembrolizumab	Pembro: 10 mg.kg Ipi: 3 mg/kg	26/278 (9%) in q2week Pembro, 32/277 (12%) in q3week Pembro, 13/256 (5%) in Ipi	5/278 (2%) in q2week, 1/277 (.450 in q2week	MR	20/278 (8%) in q2week pembro, 11/277 (4%) in q3week pembro, 1/2576 (.4%) in ipi	19/278 (7%) in q2week, 6/277 (2%) in q3week, 2/256 (2%) in ipi	NR	NR	Myositis: 2/277 (1%) in q3week, 1/256 (0.5%) in Ipi MSK stiffness: 3/278 (1%) in q2week, 2/277 (1%) in q3week
Anti-PD-1													
Borghaei 2015	3	NSLC	287	Nivolumab	3 mg/kg	46 (16%)	NR	NR	NR	18 (6%)	NR	NR	MSK pain: 39 (14%)

Author, year	Trial phase	Indication	Number exposed	Drug/s	Dose	Arthralgia	Arthritis	Dry eyes	Dry mouth	Myalgia	Muscle weakness	Vasculitis	Other
					+ 1 mg/kg nvo								
Postow 2015	1	Metastatic melanoma	142	Ipilimumab +/− Nivoluamb	Dose escalation	10/94 (10%) in combined, 4/46 (9%) in Ipi	NR	NR	NR	9/94 (10%) combined; 6/46 (13%) in Ipi	NR	NR	NR

NR: Not reported, Ipi: Ipilimumab, DE: dose escalation, Pembro: Pembrolizumab, Nivo: Nivolumab

*: Only reported grade 3 or higher adverse events.

Table 2

Description of rheumatic and musculoskeletal IRAE from included case reports and series

Author, Year	Drug	Indication	Clinical Presentation/s	Labs, imaging, and other testing	Treatment
Anti-CTLA-4					
Bostwick 2015	Ipilimumab	Metastatic melanoma	Pre-existing ulcerative colitis. Disease flared while on ipilimumab initially responding to immunosuppression but ultimately requiring urgent colectomy.	Colonoscopy after ipilimumab: erosions, ulcerations and pseudo polyps	Infliximab, Azathioprine, corticosteroids.
Conry 2015	Ipilimumab	Metastatic melanoma	Arthralgias, myalgias, fevers, progressive neurologic symptoms (ataxia, aphasia, confusion).	ANA, anti-dsDNA, RF negative	Encephalopathy responded to high dose IV corticosteroids
Fadel 2009	Ipilimumab	Metastatic melanoma	Drug induced lupus nephritis: Nephrotic range proteinuria after two injections of ipilimumab, also microscopic hematuria. Subsequent venous thrombosis of left kidney.	Positive ANA (1:100), anti-dsDNA. Biopsy with extramembranous and mesangial deposits of IgG, IgM, C3, C1q.	Prednisone 1 mg/kg and anticoagulation.
Gieliesse 2014	Ipilimumab	Metastatic melanoma	Pre-existing Crohn's disease, monitored with serial endoscopies before and during treatment.	Endoscopy before treatment showed no active inflammation; after treatment erosions and small ulcerations.	None reported.
Golstein 2014	Ipilimumab	Metastatic melanoma	Two cases of polymyalgia rheumatica/giant cell arteritis. One with scalp tenderness, headache, jaw claudication. Second patient with arthralgias, morning stiffness in shoulders, left sided facial swelling.	Both elevated CRP, one with elevated ESR Temporal artery biopsies: one with active arteritis both with intimal proliferation and disruption of elastic lamina.	Prednisone 50 mg daily and 60 mg daily.
Henderson 2015	Ipilimumab	Metastatic melanoma	Presented with conjunctival injection, foreign body sensation, limited ocular range of motion. Found to have orbital myositis.	MRI showed inflammation of extraocular muscles.	Prednisone, dose not stated.
Hunter 2009	Ipilimumab	Metastatic melanoma	Dysphagia and weakness in facial muscles, neck flexion, proximal and distal extremities.	CK > 5000 U/L. EMG showed irritable myopathy. Biopsy showed endomysial inflammatory infiltrate.	Treated with IVIG and IV methylprednisolone 1 g/day followed by prednisone 1 mg/kg and taper. Improvement of all symptoms to near baseline.
Izzedine 2014	Ipilimumab	Metastatic melanoma	2 cases of Acute Interstitial Nephritis. Pre-existing Sjogren's syndrome in one patient.	Negative ANA Renal biopsies: interstitial inflammation, tubular injury in one	Prednisone 1 mg/kg for 4 weeks followed by taper.

Author, Year	Drug	Indication	Clinical Presentation/s	Labs, imaging, and other testing	Treatment
Minor 2013	Ipilimumab	Metastatic melanoma	Uterine lymphocytic vasculitis. Presented with mass in uterus and pelvic lymphadenopathy.	Lymphocytic vasculitis involving uterine and ovarian vessels. ANA negative.	Hysterectomy due to concern for malignancy. No further treatment.
Pedersen 2014	Ipilimumab	Metastatic melanoma	Pre-existing ulcerative colitis treated with Ipilimumab. No flares while treated.	No evaluation of ulcerative colitis described.	None.
Sheikh 2015	Ipilimumab	Metastatic melanoma	Dermatomyositis. Erythematous photodistributed rash with Gottron's papules and proximal muscle weakness.	CK 1854 U/L. Aldolase 23 U/L. ANA 1: 640 speckled, anti-Jo1 negative.	Prednisone 80 mg daily tapered over 8 weeks + discontinuation of ipilimumab.
Anti-PD-1					
De Valasco 2015	Nivolumab	Metastatic renal cell carcinoma	Joint pain and stiffness in fingers, uveitis, and ultimately developed partially reducible swan neck deformities in hands.	Hand radiographs- no erosions, thought to be consistent with Jaccoud arthropathy.	None for arthropathy. Intraocular steroids for uveitis.
Yoshioka 2015	Nivolumab	Metastatic melanoma	Polymyositis with proximal muscle weakness and respiratory involvement.	CK 2812 U/L	Prednisone 30 mg daily + discontinuation of Nivolumab.
Chan 2015	Pembrolizumab	Metastatic melanoma	2 cases of polyarticular inflammatory arthritis. One involving wrist, knee, ankles. Other involving PIPs, wrist, elbow, knees.	ANA, RF, anti-CCP negative. Synovitis and tenosynovitis on MRI in both	NSAIDs in both. Pamidronate in one, hydroxychloroquine in other.
Khoja 2016	Pembrolizumab	Metastatic melanoma	Patient presented with myalgias and feeling of heaviness in muscles. Found to have eosinophilic fasciitis and encephalopathy	Elevated eosinophil count, MRI of arm with fascial edema.	Corticosteroids 1 gram daily, then taper
Manusow 2014	Pembrolizumab	Metastatic melanoma	Retinal vasculitis in the setting of ocular metastasis after pembrolizumab treatment. Not certain if was due to pembrolizumab or paraneoplastic	Fluoroscein angiography showed retinal vasculitis with leaking from vessels.	Improvement with vitrectomy

CK: creatinine kinase. ANA: antinuclear antibodies. RF: rheumatoid factor. dsDNA: double stranded DNA antibodies. CCP: cyclic citrullinated peptide antibodies. EMG: electromyography. CRP: C reactive protein. ESR: erythrocyte sedimentation rate.

Table 3

Risk of bias assessment for included clinical trials

Author, Year	Sequence generation	Allocation concealment	Blinding	Incomplete adverse event data	Selective adverse event reporting	Other
Bashey 2009	High	N/A	High	Low	Low	Low
Borghaei 2015	Low	N/A	High	Low	Low	Low
Brahmer 2010	High	N/A	High	Low	High	High
Brahmer 2012	High	N/A	High	Low	Low	Low
Brahmer 2015	Low	Low	High	Low	High	Low
Calabro 2014	N/A	N/A	High	Low	Low	High
Downey 2007	High	N/A	High	Low	Low	High
Gibney 2014	High	N/A	High	Low	Low	High
Hersh 2014	Low	Unclear	High	Low	High	Low
Hodi 2014 (1) Cancer Immunol Res	High	N/A	High	Low	Low	High
Hodi 2014 (2) JAMA	Low	Low	High	Low	High	Low
Kwon 2014	Low	Low	Low	Low	Low	Low
Larkin 2015	Low	Low	Low	Low	High	Low
Le 2013	Low	Unclear	High	Low	Low	High
Lynch 2012	Unclear	Unclear	Low	Low	Low	Low
Merchant 2015	High	N/A	High	Low	High	High
Motzer 2015	Unclear	Unclear	Low	Low	Low	Low
Postow 2015	Low	Low	Low	Low	Low	Low
Prieto 2012	High	N/A	High	Low	High	High
Ralph 2010	N/A	N/A	High	Low	Unclear	High
Reck 2013	Unclear	Unclear	Low	Low	High	Low
Ribas 2015	Low	Low	Low	Low	High	Low
Rizvi 2015	N/A	N/A	High	Low	High	High
Robert 2011	Low	Low	Low	Low	High	Low
Robert 2014	Low	Low	High	Low	High	Low
Robert 2015 (1) NEJM	Low	Low	Low	Low	Low	Low

Author, Year	Sequence generation	Allocation concealment	Blinding	Incomplete adverse event data	Selective adverse event reporting	Other
Nivo						
Robert 2015 (2) NEJM Pembro	Low	Low	Low	Low	Low	Low
Sangro 2013	N/A	N/A	High	Low	Unclear	High
Sarnaik 2010	High	N/A	High	Low	Low	Low
Weber 2008	High	N/A	High	Low	High	Low
Weber 2015	Low	Low	High	Low	High	Low
Yamazaki 2015	N/A	N/A	High	Low	Low	High
Yang 2007	High	N/A	High	Low	High	High

Nivo: Nivolumab. Pembro: Pembrolizumab.

N/A: not applicable (i.e. allocation concealment is not applicable for trials with no randomization, sequence generation is not applicable in single arm trials with only one dosing regimen). Selective adverse event includes not reporting all grades of events or not reporting all types of events on which information was collected. Other sources of bias: small size of study, stopped early, ascertainment of IRAE changed during the study.