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REVIEW

Immune checkpoint inhibitor-induced musculoskeletal manifestations

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Abstract

Immune checkpoint inhibitors (ICI) associate with a wide range of immune-related adverse events (Ir-AE), including musculoskeletal manifestations. We aimed at identifying all studies reporting musculoskeletal Ir-AE. An electronic (Medline, Scopus and Web of Science) search was performed using two sets of key words. The first set consisted of: arthritis, musculoskeletal, polymyalgia rheumatica and myositis. The second set consisted of: anti-PD-1, anti-PD-L1, anti-CTLA-4, ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab. We identified 3 prospective studies, 17 retrospective studies and 4 case series reporting 363 patients in total. Combined data from all three prospective studies provide a prevalence rate of 6.13%. Most patients were males (59.68%) and the vast majority (73%) were on programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors. Most studies report a median time of ≤ 12 weeks from first ICI administration to symptom onset. The main clinical phenotypes reported were: (a) inflammatory arthritis (57.57%), (b) myositis (14.04%) and (c) polymyalgia rheumatica (PMR) (12.12%). A total of 256 patients required steroids (70.52%) and 67 patients (18.45%) were treated with DMARDs. Positive auto-antibodies and family history of any autoimmune disease were present in 18.48% and 19.04% of cases, respectively. Only a few patients (19%) had to discontinue treatment due to musculoskeletal Ir-AE. Two prospective studies show that significantly more patients with musculoskeletal Ir-AE exhibit a favorable oncologic response compared to patients not exhibiting such manifestations whereas retrospective studies show that 77.22% of patients with musculoskeletal Ir-AE have a good tumor response. One out of 15 patients treated with ICI will develop musculoskeletal Ir-AE; in most cases the severity of these manifestations is mild/moderate and usually ICI may be continued. Rheumatologists should familiarize with this new clinical entity and develop relevant therapeutic algorithms.

Keywords Arthritis · Myositis · Polymyalgia rheumatica · Immunotherapy · Programmed death-1 · Programmed death ligand-1 · Cytotoxic T lymphocyte-associated antigen-4 · Ipilimumab · Nivolumab · Rheumatic diseases · Autoimmune diseases · Fasciitis

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Introduction

The treatment of cancer has been relying on surgery, chemotherapy and radiotherapy for decades. However, during the last years, a novel therapeutic option for cancer has emerged in the form of immunotherapy [1]. The basic concept of immunotherapy is to over activate T cells and therefore enhance their ability to attack cancer cells [2]. The use of interferon and BCG vaccine in oncology can be regarded as primitive forms of immunotherapy but their use was restrained by their limited efficacy in only certain types of cancer. A major breakthrough was the discovery of several molecules which play critical role in controlling T cell activation, known as immune checkpoints, including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) axis, among many others [3, 4]. The important role of immune checkpoints in down regulating T cell responses, acting as "natural brakes", was first depicted in animal models and it soon became apparent that these molecules could be targeted therapeutically [5]. A novel class of drugs, known as immune checkpoint inhibitors (ICI) has been developed; these drugs are monoclonal antibodies that block immune checkpoints such as CTLA-4 or PD-1. ICI act by releasing these natural brakes leading to T cell overactivation and therefore enhance antitumor immunity. ICI are currently being used in many types of cancer exhibiting remarkable clinical efficacy and an acceptable safety profile [6, 7].

Since ICI exhibit their anticancer effects by stimulating the immune system they also associate with several immune-related adverse events (Ir-AE) [8]. Any organ can be affected with most Ir-AE being mild/moderate and usually do not lead to ICI discontinuation [9]. Mild arthralgias/myalgias are relatively common in patients receiving ICI but many other musculoskeletal manifestations may occur including syndromes resembling rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) and myositis, among many others [10–14].

We performed herein a literature review of ICI-induced musculoskeletal manifestations aiming at exploring the following: (1) the prevalence of these manifestations and the time from first ICI administration to symptom onset, (2) the main clinical phenotypes and the type of treatment required to control symptoms (steroids/DMARDs), (3) the type of ICI (CTLA-4 vs PD-1/PD-L1 inhibitors) mostly associated with Ir-AE, (4) the percentage of patients with positive auto-antibodies and family history of autoimmune disease, (5) the percentage of patients requiring permanent ICI discontinuation due to musculoskeletal Ir-AE, (6) the association between musculoskeletal Ir-AE and oncologic response and (7) the risk of flare in patients with pre-existing autoimmune disease (PAD).

Search strategy

We performed an electronic search (Medline, Scopus and Web of Science) using 2 sets of key words between Jul 1 and Jul 15, 2020. The first set consisted of: arthritis, musculoskeletal, polymyalgia rheumatica and myositis. The second set consisted of: anti-PD-1, anti-PD-L1, anti-CTLA-4, ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab. We combined each term of the first set with each term of the second set. No limits were set. The computerized search was supplemented by a manual one on the reference lists of the retrieved articles. The search identified 492 articles; following removal of duplicates 249 articles remained. The abstracts of these articles were assessed to identify studies describing musculoskeletal Ir-AE. Cases of rheumatic but not musculoskeletal manifestations such as sicca, sarcoidosis and vasculitis were excluded. Studies with incomplete/insufficient data or case reports were also excluded. Sufficient data for inclusion in the analysis were: demographics (age and sex), type of immunotherapy used, time to symptom onset and a clear description of the clinical phenotype. The flowchart of the search is depicted in Fig. 1. Studies included in the analysis were reviewed in detail and data were extracted using a standardized form. Data extraction was performed independently by 2 assessors (FA and DD); each discrepancy between assessors was discussed and final decisions were reached by consensus. An additional search was performed to identify cases of patients with PAD in all retrieved articles.

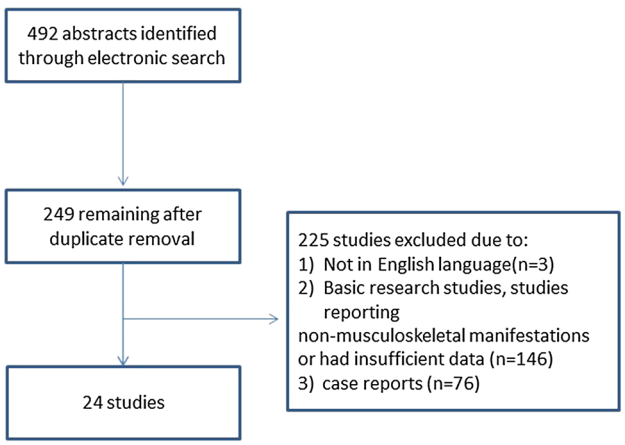

Fig. 1 Flowchart of the search

Results

The review identified 3 prospective studies, 17 retrospective studies and 4 case series reporting 363 cases in total.

Prospective studies

Only 3 prospective studies have been published so far in this rapidly evolving field. The largest one [11], is a 2-year observational study aiming at exploring the clinical characteristics of rheumatic Ir-AEs as well as their association with tumor response. During this period 35 patients out of 524 receiving ICIs, developed musculoskeletal symptoms (prevalence 6.6%). The vast majority ($n=34$) received PD-1/PD-L1 inhibitors and the median time to symptom onset was 70 days. Twenty out of the 35 patients were diagnosed with inflammatory arthritis; in these patients, clinical presentation matched one of three characteristic phenotypes: RA, PMR and psoriatic arthritis (PsA). Specifically, 7 patients developed RA-like manifestations with symmetrical hand involvement. All these patients received steroids at low/moderate doses and all experienced improvement or complete resolution of their symptoms. Steroids were progressively tapered but after a 6-month follow up only 2 patients were able to discontinue treatment. Eleven patients developed a PMR-like syndrome with increased CRP in 7/11 patients. Two patients, one of whom had pre-existing psoriasis, were diagnosed with PsA. They were treated with NSAIDs while one required the addition of methotrexate (MTX). In general, all patients responded well to treatment and only one had to temporarily discontinue immunotherapy. The authors also reported non-inflammatory musculoskeletal symptoms in 15 patients that were exacerbated by physical strain and relieved by rest. The predominant complaint of all these patients was arthralgia of proximal or distal joints, mostly shoulders and hands, while 5 patients reported concurrent back pain. All patients were managed with opioids/analgesics and physiotherapy.

An important finding of this study was that patients experiencing rheumatic Ir-AEs had higher tumor response rates compared to patients without Ir-AEs (85.7% vs 35.3% for patients with musculoskeletal Ir-AE vs patients without, respectively, $p<0.0001$).

This is the largest prospective study to date and the first to report non-inflammatory musculoskeletal symptoms as an adverse event of immunotherapy.

In our department, we have recently reported the results of a prospective clinical and MRI study of ICI-induced musculoskeletal manifestations [10]. During a period of 2 years, 130 patients were started on ICI treatment in the Oncology Department of our hospital. Of those, 10 developed ICI-induced musculoskeletal manifestations (prevalence 7.7%) with a median time to symptom onset of 2.5 months. Three distinct clinical patterns were recognized. Prominent joint involvement was found in three patients; two developed an RA-like pattern of arthritis of small joints of hands and one oligoarthritis of lower limbs. MRI performed in the patient with oligoarthritis revealed synovitis and fasciitis around the involved joint. Marked periarticular involvement was found in 4 patients with diffuse swelling of the hands, feet or knees. MRI depicted tenosynovitis with more pronounced myositis and/or fasciitis in surrounding tissues in all patients. Three patients presented clinically with pain in the knee(s) or thigh(s) with no associated muscle weakness and normal serum CPK levels. MRI depicted myofasciitis of the surrounding muscles in all cases. One of these patients was subjected to a muscle and fascia biopsy on the site of highest intensity signal in MRI to rule out malignancy. The biopsy showed chronic inflammatory infiltration of both muscle and fascia.

Our study was the second one to systematically explore the potential association between musculoskeletal Ir-AE and oncologic response. We also found a higher tumor response rate in the rheumatic Ir-AE group compared to the non Ir-AE group (50% vs 12.5%, respectively, $p=0.0016$).

Our data show that myofasciitis is the prominent imaging finding in most patients indicating that the synovium may be less frequently involved than the muscle/fascia. These data point to the direction that these manifestations are part of a novel clinical entity with clear differences with known rheumatic diseases such as RA and PMR. A multicenter, clinical and MRI study of ICI-induced musculoskeletal manifestations is currently running and may provide more details regarding the tissues involved [15].

In the third prospective study the authors explored the development of rheumatic Ir-AEs following the administration of PD-1 inhibitors in a single center [12]. Eleven patients out of the 210 receiving immunotherapy developed rheumatic Ir-AE in a 2-year timeframe (prevalence 5%). The median time to symptom onset was 8 weeks. Musculoskeletal Ir-AEs reported were oligo- or polyarthritis ($n=5$), PMR-like syndrome ($n=1$) and symptomatic inflammatory myositis with fasciitis ($n=2$). Clinical presentation varied across patients experiencing oligo- or polyarthritis, affecting both small and large joints. All patients responded partially or completely to treatment with NSAIDs, steroids or DMARDs with only one patient discontinuing ICI therapy due to adverse events. Two patients presented with inflammatory myositis and fasciitis, confirmed by MRI that manifested clinically as muscle aches and heaviness of lower extremities. In both patients ICI therapy was discontinued

due to cancer progression leading to rapid resolution of their symptoms.

Retrospective studies

The search identified 17 retrospective studies which are presented in Table 1 [16–32]. A summary of all these studies is provided in Supplemental data.

The search also identified four case series [33–36] that report eight patients with inflammatory arthritis/PMR ($n=6$) as well as two patients with temporal arteritis.

Outcomes of ICI treatment in patients with pre-existing autoimmune disease (PAD)

We identified eight relevant retrospective studies specifically designed for this purpose.

The largest analysis so far regarding the safety of PD-1 inhibitors in patients with PAD has been performed by the Food and Drug Administration (FDA). They identified 552 cases of patients with PAD in 22 clinical trials. Most patients had autoimmune thyroiditis or vitiligo and none was receiving steroids at baseline. PAD worsening was not frequently reported, ranging from 6 to 16% according to the ICI used [37]. The data derived from this study are certainly encouraging indicating that ICI may have an acceptable safety profile in patients with PAD. However, we should note that most patients in this study had mild, organ specific PAD and therefore these results cannot be extrapolated to patients with more severe, systemic forms of PAD.

Data that appear more relevant to rheumatologists were reported in a retrospective analysis on the safety and efficacy of immunotherapy in patients with PAD using three national networks [38]. The authors reviewed the development of PAD flares, new Ir-AEs and tumor response. Overall, 112 patients were included in this study and 79 (71%) experienced toxicity in the form of PAD flare ($n=53$), other Ir-AE ($n=47$) or combination of both ($n=20$). The most frequent PAD in this study were psoriasis and PsA ($n=31$), RA ($n=20$), inflammatory bowel disease ($n=14$) but a few cases of PMR/GCA ($n=7$), spondyloarthropathy ($n=5$) and systemic lupus erythematosus (SLE, $n=4$) were also reported. Among patients experiencing a PAD flare, 28 required immunosuppression. Steroids were used in 24, DMARDs in 6 and TNF blockers in 3. Forty seven patients developed a new Ir-AE unrelated to their primary autoimmune disease. Of those, 24 required steroids, 1 was treated with MTX and I with TNF blocker. Forty eight patients in total (43%) required immunosuppression mostly in the form of steroids. The authors reported 28 patients with several immune mediated diseases such as Sjogren syndrome, ANCA vasculitis, dermatomyositis among many others. None of these patients experienced a disease flare. It is noteworthy that four patients with SLE tolerated ICI treatment well with no need for additional immunosuppression or immunotherapy discontinuation. The authors also report that patients receiving immunosuppressive therapy at baseline had a shorter median progression free survival (3.8 versus 12 months; $p=0.006$).

There are several other studies assessing the safety of immunotherapy in patients with PAD [39–44], reporting a PAD flare rate ranging between 27 and 42% indicating that ICI may be relatively safe. Of note, in most cases immunotherapy was continued.

Additionally, we identified five retrospective studies assessing de novo rheumatic Ir-AE which also report data regarding PAD flares [21, 27, 30, 32, 45] as well as two relevant case reports [46, 47]. These studies are summarized in Supplemental Data.

Data indicate that the majority of patients with PAD will develop either a PAD flare or another Ir-AE. However, most manifestations reported were mild/moderate and could be managed with immunosuppressants with most patients not requiring ICI discontinuation. Therefore, oncologists should not avoid administering ICI to patients with PAD, if they feel that this treatment is the most appropriate, under close monitoring.

Following analysis of data presented above we next address several issues regarding ICI-induced musculoskeletal manifestations.

What is the prevalence of these manifestations?

Prevalence is more accurately depicted from prospective studies; the 3 available such studies report prevalence rates ranging from 5 to 7.7%. Combined data from all 3 studies provide a prevalence rate of 6.13%. By adding data derived from 3 retrospective studies that report relevant data the prevalence rate slightly increases to 6.71%. Therefore, approximately 1 out of 15 patients under ICI treatment may require assessment/treatment by a rheumatologist. Data regarding gender could not be extracted from 4 retrospective studies and were excluded from analysis. All the other studies report a total of 258 patients of whom 154 were male (59.68%) indicating that ICI-induced musculoskeletal manifestations appear to be slightly more common in men than women.

What is the time from the first ICI administration to symptom onset?

Seventeen out of the 20 available prospective and retrospective studies report median time from first ICI administration to symptom onset which ranges from 4 to 38 weeks. However, the majority of studies (9/15, including all 3 prospective studies) report a median time of ≤ 12 weeks

Table 1 Studies reporting musculoskeletal Ir-AE

Study Author (REF)	Pts (*n*)	Median time to symptom onset (weeks)	Inflammatory arthritis	Mono/oligo arthritis	polyarthritis	PMR	Myositis	Treatment with steroids	Initial steroid dose ≥ 20 mg	DMARDs	ICI D/C
Kostine et al. [11]	**35**	**10**	**9**	**(–)**	**(–)**	**11**	**0**	**16**	**(–)**	**2**	**0**
Daoussis et al. [10]	**10**	**10**	**7**	**(–)**	**(–)**	**0**	**3**	**6**	**0**	**0**	**0**
Narvaez et al. [12]	**8**	**8**	**5**	**1**	**4**	**1**	**2**	**5**	**5**	**3**	**0**
Richter et al. [16]	47	(–)	34	12	22	3	10	38	(–)	5	12
Le Burel et al. [17]	20	8.1	13	0	13	4	3	19	13	3	6
Cappelli et al. [19]	30	(–)	30	(–)	(–)	0	0	24	(–)	3	(–)
Budar et al. [26]	26	14.3	10	5	5	0	0	6	(–)	1	(–)
Mitchell et [27]	24	17.9	18	6	12	2	3	19	(–)	9	8
Zimmer et al. [28]	21	(–)	2	(–)	(–)	2	4	10	6/7	0	(–)
Moreira et al. [29]	22	19	0	0	0	3	19	18	(–)	0	14
Calabrese et al. [30]	11	7.3	7	(–)	(–)	3	1	11	8/9	3	8
Leipe et al. [31]	16	20	14	12	2	0	0	8	(–)	6	0
Liew et al. [32]	12	24	11	(–)	(–)	1	0	9	(–)	3	2
Lidar et al. [18]	13	(–)	12	2	10	0	0	13	(–)	8	3
Cappelli et al. [25]	9	(–)	9	0	9	0	0	7	5	2	0
Belkhir et al. [20]	10	4	6	(–)	(–)	4	0	7	4	3	1
Mooradian et al. [21]	12	38	10	(–)	(–)	2	0	10	(–)	9	2
Smith and Bass [22]	10	5.5	10	6	4	0	0	10	6	4	1
Lee et al. [24]	11	9	(–)	(–)	(–)	(–)	(–)	7	5	0	6
Shah et al. [23]	6	5.4	0	0	0	0	6	5	5	0	3

Prospective studies in bold

D/C: Permanent discontinuation due to musculoskeletal Ir-AE

indicating that musculoskeletal ICI-induced Ir-AE most often appear within the first trimester of immunotherapy.

What are the main clinical phenotypes?

The main clinical phenotypes reported were: (a) inflammatory arthritis (209 cases, 57.57%), including cases described as "RA-like", seropositive and seronegative RA, PsA and inflammatory arthritis. Details regarding the pattern of joint involvement could be recorded from 10 studies; 45 cases (35.4%) were described as monoarticular or oligoarticular and 82 cases (64.6%) as polyarticular, (b) myositis (51 cases, 14.04%), including cases described as myopathy, inflammatory myopathy and myositis. Many patients with ICI-induced myositis had painful syndromes whereas some of them had normal CPK levels, features that are not compatible with typical polymyositis and (c) PMR (44 cases, 12.12%), including cases described as PMR or "PMR-like". A total of 256 patients required steroids for musculoskeletal Ir-AE (70.52%-patients receiving steroids for other concurrent Ir-AE were excluded) and 67 patients (18.45%) were treated with DMARDs.

The most frequently used DMARD was MTX, however a recent study reported that hydroxychloroquine may be an effective and safe alternative [48]. According to clinical phenotype, in cases of inflammatory arthritis 148 patients out of 185 with available data required steroids (80%). In cases of PMR 40/43 with available data were treated with steroids (93.02%); of those, 18 (45%) required an initial prednisone dose $\geq$ 20 mg. The striking heterogeneity of ICI-induced myositis is also underscored in the therapies applied. One out of five patients had mild disease that did not even require steroids whereas several patients had severe symptoms requiring high dose steroids. More specifically, 40/51 cases were treated with steroids (78.43%); of those, 23 (57.5%) required a prednisone dose $\geq$ 20 mg.

Is there an ICI type (CTLA-4 vs PD-1/PD-L1 inhibitors) mostly associated?

From the 363 patients reported in total, 265 were treated with PD-1/PD-L1 inhibitors (73%) in sharp contrast to only 11 (3.03%) with CTLA-4 inhibitors with the rest patients receiving combination immunotherapy. There is a striking over-representation of patients treated with PD-1/PD-L1 inhibitors among reported patients with ICI-induced musculoskeletal Ir-AE indicating that this form of treatment may be more tightly linked to these manifestations. However, definite conclusions cannot be drawn from these data because PD-1/PD-L1 inhibitors were more widely used in all studies.

What is the percentage of patients with positive auto-antibodies or with a family history of autoimmune disease?

Positive auto-antibodies (defined as positive ANA and/or RF and/or ACPA) were found in 39 out of 211 patients tested (18.48%, data available from 15 studies). A family history of any autoimmune disease was reported in 16 out of 84 patients (19.04%, available data from 5 studies).

What is the percentage of patients requiring permanent ICI discontinuation due to musculoskeletal Ir-AE?

We identified 69 cases (19%) that had to discontinue treatment due to musculoskeletal Ir-AE indicating that in most cases musculoskeletal Ir-AE could be managed successfully.

Is there an association between musculoskeletal Ir-AE and oncologic response?

Only prospective studies can provide comparative data regarding tumor response between patients developing and not developing musculoskeletal Ir-AE and therefore may lead to more definite conclusions. Two prospective studies show that significantly more patients with musculoskeletal Ir-AE exhibit a favorable oncologic response (defined as complete response, partial response or stable disease) compared to patients not exhibiting such manifestations. Retrospective studies show that out of 180 patients with available data (derived from 16 studies) 139 (77.22%) had a good response providing further evidence that musculoskeletal Ir-AE may predict a favorable oncologic response.

ICI-induced musculoskeletal manifestations: prevalence, main clinical phenotypes and differences with their idiopathic counterparts

Our review led to several conclusions with clinical significance. Musculoskeletal Ir-AE develop approximately in 1 out of 15 patients under ICI; it appears that these manifestations are slightly more common in men than women. Most relevant studies report that musculoskeletal Ir-AE develop within the first 3 months from initiation of immunotherapy, a common finding for most Ir-AE. The spectrum of musculoskeletal Ir-AE is wide with significant heterogeneity; this was apparent in most studies reporting relevant data. However, three main clinical phenotypes were mostly recorded: inflammatory arthritis, myositis and PMR. Of note, a recent, large scale multicenter study also showed that these phenotypes are most frequently encountered [49]. In cases of ICI-induced inflammatory arthritis one should note several

differences with RA. The vast majority of cases did not have auto-antibodies whereas most cases were effectively treated with steroids alone, something not usually seen in RA. The low frequency of auto-antibodies in ICI-induced arthritis was recently depicted in a retrospective comparative study [50].

The differences between ICI-induced myositis and classic polymyositis are more pronounced. ICI-induced myositis appears to have a wide spectrum ranging from mild syndromes that do not even require steroids to severe life-threatening manifestations [51]. Recent evidence indicate that several patients may have bulbar symptoms or oculomotor impairment and exhibit overlapping features with myasthenia gravis and myocarditis [52]. There are also differences at the histology level with necrosis and macrophage infiltration being prominent features in ICI-induced myositis [53]. ICI-induced PMR also appears to manifest several differences with classic PMR such as the highest frequency of peripheral joint involvement [54]. However, an imaging study did not detect major differences between ICI-induced and classic PMR [55]. The above data point to the direction that musculoskeletal Ir-AE should not be regarded as "RA-like", polymyositis-like" or "PMR-like" diseases but as novel clinical entities with significant heterogeneity that should be studied carefully and described in more detail in future large scale studies.

ICI-induced non-inflammatory musculoskeletal manifestations: a clinical entity that requires further evaluation

Several studies report cases of non-inflammatory musculoskeletal manifestations or painful syndromes in areas already affected by osteoarthritis providing further evidence that these manifestations are heterogeneous [11, 49]. The prevalence of these manifestations may be higher since they are relatively mild, cause less functional impairment and therefore are less likely to be recorded/diagnosed. We expect that in the near future these manifestations will be recorded more often taking into account that the number of cancer patient under immunotherapy evaluated by rheumatologists is constantly increasing.

Treatment options for ICI-induced musculoskeletal manifestations

Another finding of our analysis is that 7/10 patients with musculoskeletal Ir-AE will require treatment with steroids. DMARDs do not seem necessary for the majority of patients since less than 20% required the addition of a DMARD, usually due to relapse during tapering of steroids. Biologics, mostly in the form of TNFα blockers have been used successfully in a limited number of cases refractory to conventional treatment. Of interest, increased TNFα expression in the synovium of a patient with ICI-induced arthritis has been reported indicating that TNF blockers may be the most suitable biologic [56].

In most cases musculoskeletal Ir-AE can be managed successfully; permanent ICI discontinuation due to musculoskeletal Ir-AE is needed in less than 20% of cases.

Immunotherapy type and musculoskeletal manifestations

Inhibitors of the PD-1/PD-L1 axis appear to be more tightly linked to musculoskeletal Ir-AE compared to CTLA-4 inhibitors. It was apparent from the initial ICI trials that anti-PD-1 compared to anti-CTLA-4 agents did not have the same profile of adverse events with musculoskeletal manifestations being more prominent in anti-PD-1 drugs. These clinical observations were in agreement to data from animal models; only PD-1 and not CTLA-4 knockout mice develop arthritis [3, 4].

Autoantibodies, family history of autoimmune diseases and pre-existing autoimmune diseases

Most patients with musculoskeletal Ir-AE do not have autoantibodies or a family history of autoimmune disease. However, approximately 20% have either auto-antibodies or a positive family history, percentages higher than those in the general population. These data indicate that there may a be a genetic predisposition for these manifestations. It remains to be explored whether patients with auto-antibodies prior to ICI treatment are prone to develop a more severe or chronic disease that persists despite ICI discontinuation [57]. Currently we do not know which patients will develop chronic symptoms. Of interest, a recent study showed that persistence of ICI-induced arthritis mainly associates with longer ICI use, combination immunotherapy and development of multiple other Ir-AE [58].

A major challenge for oncologists is whether administration of immunotherapy is safe in cancer patients with PAD. Existing evidence points to the direction that ICIs are generally well tolerated in patients with PAD. This population definitely carries an increased risk with 7/10 patients exhibiting some form of toxicity either in the form of a PAD flare or development of a de novo Ir-AE [38]. However, most cases can be managed successfully and immunotherapy regimens can be completed. Therefore, there is no evidence to suggest that these patients should not be treated with ICI if

needed. It would be reasonable, however, to avoid combination immunotherapy in patients with severe PAD. Another issue which is of interest for oncologists is the link between musculoskeletal Ir-AE and favorable oncologic response; this link has been verified in two prospective studies so far. These data indicate that musculoskeletal Ir-AE may serve as a prognostic marker of response to immunotherapy. Therefore, these manifestations should be treated effectively so patients may continue immunotherapy.

Strengths and limitations of the study

Our study has several strengths and limitations. A strength of the study is the fact that it focuses on specific questions with major clinical significance which have not been adequately addressed so far, such as the necessity of immunotherapy discontinuation or the potential association of ICI-induced musculoskeletal syndromes and tumor response. A limitation of the study is that the meta-analysis was based on a search solely in Medline using a limited set of keywords and therefore some relevant studies might have been missed.

Conclusions

Musculoskeletal Ir-AE are not uncommon and most frequently appear in the form of arthritis, myositis or PMR. ICI-induced musculoskeletal syndromes exhibit several differences with their idiopathic counterparts indicating that they represent novel clinical entities that should be studied in detail further. Rheumatologists should familiarize with these novel syndromes and develop relevant therapeutic algorithms.

Author contributions FA performed the literature search, extracted data from the retrieved articles, analyzed the data and assisted in manuscript drafting. DB, TD and LS assisted in the design of the study, data analysis and manuscript drafting. DD conceived the idea and designed the study, extracted data from the retrieved articles, analyzed the data and drafted the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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