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Review

Rheumatic immune related adverse events in patients treated with checkpoint inhibitors for immunotherapy of cancer

Gian Domenico Sebastiani[a], Chiara Scirocco[a,*], Mauro Galeazzi[b]

[a] Rheumatology Unit, Azienda Ospedaliera San Camillo – Forlanini, Rome, Italy
[b] Rheumatology Institute, University of Siena, Italy

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ABSTRACT

Immune checkpoints are small molecules expressed by immune cells that play critical roles in maintaining immune homeostasis. Immune checkpoint inhibitors (ICPIs) are new cancer drugs that target self-tolerance pathways exploited by tumors to escape immune destruction, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand (PD-L1). Several ICPIs have been approved by Food and Drug Administration, increasing overall survival with different cancers. However, their use can determine development of many different inflammatory side effects, that are defined immune-related adverse effects (irAEs); among others, rheumatological irAEs can develop in these patients. Currently, we have limited data about these adverse effects; particularly, few evidence come from clinical trials about patients with pre-existing autoimmune diseases because they were excluded from them. Therefore we analysed the existing scientific literature dealing with this issue, in order to answer to different clinical questions. According to all reviewed data, rheumatological irAEs are not infrequent, in both previously diseased and undiseased patients, but they are often mild and reversible. Close monitoring and interdisciplinary management and monitoring is necessary in order to ensure best care. Many questions remain unanswered or not completely answered; further data are necessary to implement our knowledge in this field and to standardize and optimize clinical practice.

1. Introduction

Immune checkpoints are small molecules expressed by immune cells that play critical roles in maintaining immune homeostasis. Antigen signaling by T-cell receptor (TCR) alone is not sufficient to fully activate the T cells. On its own, TCR cross-linking can trigger anergy, a non-responsive state in which T cells are resistant to subsequent activation. T cell activation requires a second signal delivered by costimulatory molecules expressed on the cell surface.

The best characterized costimulatory signal is released by CD28. The classical ligands for CD28 (CD80/CD86) are expressed on the surface of antigen presenting cells (APCs) such as dendritic cells, monocytes, and B cells. Furthermore, the activation signals triggered by TCR binding are balanced by inhibitory signals that dampen T cell activation. For example, the inhibitory receptor cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) competes for the same ligands as CD28 (CD80 or CD86 expressed on APCs) and antagonizes TCR signaling. Thus, CD28 is a critical costimulatory molecule that is activated by its ligands, CD80 and CD86, whereas CTLA-4 is a cell surface receptor whose ligands are CD80 and CD86 too, which participates in lower affinity interactions with the costimulatory T cell receptor CD28. CTLA-4 functions as an inducible receptor with T cell inhibitory activity, and its primary role is to down-regulate T cell activation [1–4]. Blockade of this inhibitory receptor with drugs such as ipilimumab is used to treat different types of cancer [5]. On the other hand, the immunomodulatory drug abatacept (CTLA4-Ig) works by blocking CD28-dependent costimulatory signals, and is used in the treatment of rheumatic diseases such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA).

Another important inhibitory receptor is programmed cell death 1 (PD-1). It is induced in T cells in patients with chronic viral infections, while blockade of PD-1, or its ligand PD-L1, is useful in the treatment of cancer [6].

Cancer immunotherapy is a treatment modality used to mobilize the immune system to recognize and destroy cancer cells. Immune checkpoint inhibitors (ICPIs) have been developed to target self-tolerance pathways that are exploited by tumors to escape immune recognition and destruction.

To date, 6 ICPIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of a broad spectrum of

* Corresponding author at: Rheumatology Unit, Azienda Ospedaliera San Camillo – Forlanini, Circonvallazione Gianicolense, 87 – 00152 Rome, Italy.
E-mail addresses: GSebastiani@scamilloforlanini.rm.it (G.D. Sebastiani), chiascir@hotmail.it (C. Scirocco).

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Table 1
Immune checkpoint inhibitors approved by Food and Drug Administration.

Immune checkpoint inhibitors antibodies approved by the Food and Drug Administration[a]		
Drug	Action	Indication
Ipilimumab	Anti-CTLA-4	Melanoma
Nivolumab	Anti-PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	Anti-PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	Anti-PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	Anti-PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	Anti-PD-L1	Urothelial carcinoma

[a] CTLA-4 = cytotoxic T-lymphocyte antigen 4, PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1.

malignancies, and many others are going to be approved. Ipilimumab is a CTLA-4 inhibitor; nivolumab and pembrolizumab are anti–PD-1 agents; and atezolizumab, durvalumab, and avelumab are anti-PD-L1 agents. Targeting the immune checkpoints CTLA-4 and PD-1 with inhibitory antibodies has demonstrated effective and durable antitumor activity in subgroups of patients with cancer. As an example, ipilimumab has been approved by FDA and European Medicines Agency (EMA) for treating metastatic melanoma (MM). The ICPIs nivolumab, pembrolizumab and atezolizumab have been FDA and EMA approved for treating MM and non-small cell lung cancer (NSCLC) [7,8] (Table 1).

However, as a result of activation of the immune system, several immune-related adverse events (irAEs) have emerged following ICPIs therapy, such as endocrine, neurological, gastroenteric, dermatologic, ocular, hepatic, renal, and rheumatic ones.

Currently, we have limited data coming from clinical trials about rhematological irAEs in patients treated with ICPIs; particularly, there are few evidences concerning ICPI therapy in patients with pre-existing autoimmune-inflammatory rheumatic diseases (ARDs). This is due to the fact that this condition has been an exclusion criterion in all clinical trials, given that autoimmune toxicity could be exacerbated.

Thus, the population of patients affected by ARDs, is a special one. In fact, in real life, these “inheligible patients” are frequently not excluded from ICPI treatment but have to be managed with these drugs because the clinical priority is obviously the treatment of cancer.

Taking into account that rheumatic irAEs are closely linked to the mechanisms of action of ICPIs on immune cells, we can expect many rheumatic irAEs or exacerbations of rheumatic symptoms considering the future worldwide prescription of ICPI; this represents a challenging question for academic and community onchologists and rheumatologists.

Therefore, the objective of the present study was to analyze the existing scientific literature dealing with the complex interrelationship between ICPIs treatment and ARDs, in order to give an answer to the following clinical questions:

1) May ICPI therapy induce the onset of a ARD in previously undiseased patients?
2) May ICPI affect the disease course of ARDs or, in other words, may ICPI induce the onset of rheumatic irAEs in patients already affected by ARD?
3) How to treat the patient who develops rheumatic irAEs following ICPI treatment? Has ICPI therapy to be discontinued?
4) Do predictive factors of increased risk of rheumatic irAEs exist?

2. Methods

A search of the medical literature was executed using MEDLINE and PubMed databases, starting from January 1st 2012 (the first report of objective response to PD-1 blockade by Topalian et al. appeared in 2012 [8]) until November 30th 2018, looking for studies reporting information on patients affected by autoimmune/inflammatory rheumatic diseases [systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren syndrome (SjS), RA, PsA, ankylosing spondylitis (AS), polymiositis/dermatomyositis (PM/DM), polymyalgia rheumatica (PMR)], treated by ICPIs for emerging neoplastic diseases, and for rheumatic irAEs caused by cancer immunotherapy. The main MeSH search phrase – any of the above reported ARDs – was paired with other search terms including nivolumab, ipilimumab, pembrolizumab, durvalumab, atezolizumab, avelumab, PD-L1/PD-1, immunotherapy, combination immunotherapy, immunotherapy adverse events, and immune related adverse events. Additional papers were retrieved by reviewing the articles for accuracy.

All articles reviewed and commented are reported in the Tables 2a, 2b, 2c, 2d.

3. Results

Finally, 28 paper have been selected.

All the papers analysed according to the clinical question, are reported in the Tables 2a, 2b, 2c, 2d, identified by first author, year, country, study design, number of patients and type of ICPI.

3.1. May ICPIs induce the onset of an ARD in previously undiseased patients?

ICPIs can induce a wide variety of irAEs, in previously undiseased patients.

Among others, rheumatological irAEs are not infrequent, but they have to date not been widely recognized and characterized [9].

In this section we analyze different papers which have addressed and reported about this kind of AE.

Beck et al. in an observational retrospective study, reported on 198 patients with metastatic melanoma or renal cell carcinoma treated with ipilimumab [10]. Although enterocolitis was the most common grade 3/4 immune-mediated toxicity seen with ipilimumab, 4 patients (2%) developed arthritis.

Bronstein et al. conducted a similar retrospective review of 119 patients (84 men, 35 women) with advanced metastatic melanoma who had undergone anti–CTLA-4 therapy [11]. Their purpose was to review the radiographic manifestations of anti–CTLA-4–related adverse events and to evaluate the possible association between the incidence of radiologic manifestations of irAEs and response to treatment. Among 119 study patients, 20 patients (16.8%) were found to have radiographic abnormalities potentially explained by irAEs, including colitis in 6 patients, hypophysitis in 2 patients, arthritis in 4 patients (seen as increased FDG uptake in the synovia of multiple bilateral peripheral joints on PET images or as joint effusion or as bilateral sacroiliitis), and thyroiditis with severe ophthalmopathy in a patient. Radiographic findings included clinically silent abnormal intramuscular

Table 2a
Papers analysed according to clinical question 1

First Author	Year	Country	Study design (study name)	Patients	Drug target
Beck KE	2006	USA	Observational retrospective study	198 patients	Anti-CTLA-4
Bronstein Y	2011	USA	Observational retrospective study	119 patients	Anti-CTLA-4
Fadel F	2009	France	Case report	1 patient	Anti-CTLA-4
Goldstein BL	2014	USA	Case series	2 patients (without ARD)	Anti-CTLA-4
Calabrese C	2017	USA	Case series	15 patients (13 without, 2 with ARD)	Anti-CTLA-4, anti-PD-1, anti-PD-L1
Belkhir R	2017	France	Observational retrospective study	10 patients	Anti-PD-1, anti-PD-L1
Suarez-Almazor ME	2017	USA	Case series	2 patients	Anti-PD-1
Cappelli LC	2017	USA	Case series	13 patients	Anti-CTLA-4, anti-PD-1
Cappelli LC	2017	USA	Systematic literature review	NA (52 papers)	Anti-CTLA-4, anti-PD-1
Le Burel S	2017	France	Observational retrospective study	447 patients	Anti-PD-1, anti-PD-L-1
Le Burel S	2017	France	Observational retrospective study	908 patients (without ARD)	Anti-PD-1, anti-CTLA-4
Moseley KF	2018	USA	Retrospective case Series	6 patients	Anti-CTLA-4, anti-PD-1

hyperenhancing foci and increased FDG uptake suggestive of myositis in 2 patients, and symmetric bilateral hilar and mediastinal sarcoid-like lymphadenopathy in 8 patients. These radiologic manifestations were noticed 2–26 months (median, 6.3 months) after the initiation of treatment. Anti–CTLA-4 treatment was terminated in two patients because of severe toxicity, whereas it was continued in 18 patients. Of these, in 11 patients, the radiologically evident irAEs resolved completely within 6 months despite continuation of anti–CTLA-4 treatment; in 9 patients the adverse effect decreased slowly, but persisted through the entire course of therapy. Interestingly, patients with radiologic manifestations of irAEs had a better response to cancer immunotherapy then patients without radiologic manifestations of irAEs.

Belkhir et al. reported a series of 10 patients in whom seropositive RA or PMR developed after ICPI treatment [12]. Patients were included if they had received ipilimumab, nivolumab, pembrolizumab or another ICPI in development and, after treatment, had a diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [13] or PMR according to the 2012 EULAR/ACR [14]. Six patients developed a seropositive RA and 4 developed PMR. The mean age of patients was 65 years and 60% were male. The median time to irAE appearance after ICPI exposure was 1 month (range 1–9 months). All cases of RA and PMR occurred after anti-PD-1 treatment, suggesting an important role of the PD-1/PDL-1 pathway in RA and PMR pathogenesis. Additional cases of PMR after anti-PD-1 treatment have been reported [15].

Indeed, 2 cases of PMR after ipilimumab were also reported, suggesting that the CD80/86 – CTLA-4 pathway may be involved in the pathogenesis of this disease as well [16].

Calabrese et al. reported a series of patients evaluated at the Cleveland Clinic Foundation from 2015 to 2016 with rheumatic irAEs as a result of cancer immunotherapy, as well as patients with a pre-existing ARD who were evaluated pre-emptively [17]. In the group of 13 patients without a previous diagnosis of ARD 7 patients developed inflammatory arthritis (IA), tree PMR-like syndrome, five sicca syndrome and one myositis (there were patients with more than one irAE). The median time to onset of irAE was 7.3 weeks (range 2–48.4). Autoimmune testing showed the presence of various autoantibodies, including ANAs, anti-dsDNA, RF, anti-SSA (Ro), in some cases.

Cappelli et al. reported on 13 patients referred by oncologists to the Johns Hopkins Rheumatology clinics from 2012 to 2016 because identified as having new rheumatological symptoms in the context of treatment with ipilimumab and/or nivolumab for NSCLC, MM or renal

Table 2b
Papers analysed according to clinical question 2.

First Author	Year	Country	Study design (study name)	Patients included	Drug target
Johnson DB	2016	USA	Observational retrospective study	30 patients	Anti-CTLA-4
Gutzmer R	2017	Germany	Retrospective multicentre study	41 patients (with previous AID/anti-CTLA4 irAEs)	Anti-PD-1
Calabrese C	2017	USA	Case series	15 patients (13 without, 2 with ARD)	Anti-CTLA-4, anti-PD-1, anti-PD-L1
Weinstock C	2017	USA	Observational retrospective study	522 patients (with ARD)	Anti-PD-1, anti-PD-L1
Menzies AM	2017	Australia	Observational retrospective study	52 patients with ARD; 67 with toxicity with anti-CTLA-4)	Anti-PD-1
Abdel-Wahab N	2018	USA	Systematic Review	123 patients	Anti-PD-1, anti-CTLA-4
Danlos FX	2018	France	Observational retrospective study	45 patients	Anti-PD-1
Leonardi GC	2018	USA	Observational retrospective study	56 patients	Anti-PD-L1
Maul LV	2016	Germany	Case report	1 patient (with ARD)	Anti-PD-1

Table 2c
Papers analysed according to clinical question 3.

First Author	Year	Country	Study design (study name)	Patients included	Drug target
Spain L	2016	United Kingdom	Review	NA	Anti-PD-1, anti-CTLA-4
Naidoo J	2017	Germany	Expert opinion	NA	NA
Belkhir R	2017	France	Observational retrospective study	10 patients (without ARD)	Anti-PD-1, anti-PD-L1
Calabrese C	2017	USA	Case series	15 patients (13 without, 2 with ARD)	Anti-CTLA-4, anti-PD-1, anti-PD-L1
Gutzmer R	2017	Germany	Retrospective multicentre study	41 patients (with previous AID/anti-CTLA4 irAEs)	Anti-PD-1
Le Burel S	2017	France	Observational retrospective study	908 patients (without ARD)	Anti-CTLA-4, anti-PD-1
Menzies AM	2017	Australia	Observational retrospective study	52 patients with ARD; 67 with toxicity with anti-CTLA-4)	Anti-PD-1
Moseley KF	2018	USA	Retrospective Case Series	6 patients (without ARD)	Anti-CTLA-4, anti-PD-1
Abdel-Wahab N	2018	USA	Systematic Review	123 patients	Anti-CTLA-4, anti-PD-1
Danlos FX	2018	France	Observational retrospective study	45 patients	Anti-PD-1
Leonardi GC	2018	USA	Observational retrospective study	56 patients	Anti-PD-L1
Esfahani K	2017	Canada	Case report	1 patient	Anti-PD-1

cell carcinoma [9]. Nine of them developed IA. The clinical presentation was variable between these 9 patients and involved both large and small joints in the upper and lower extremities. No patients with IA were positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies, while 3 had ANA positivity. Four patients had sicca symptoms: all 4 presented with the relatively abrupt onset of severe dry mouth symptoms and had severe salivary hypofunction. A patient had concurrent bilateral parotid gland swelling which resolved with steroid therapy. Three of the sicca patients had ANA, a patient had anti-La (SSB) antibodies, and a patient was RF-positive; a patient had anti-EJ antibodies (one of the anti-synthetase antibodies), without Raynaud's phenomenon, cutaneous rash or evidence of myositis.

The same author (Cappelli) performed a systematic literature review identifying 52 papers containing information about musculoskeletal or rheumatic irAEs as a consequence of ICPI treatment [18]. Of these 52 papers, 33 were clinical trials, 3 were observational studies, and 16 were case reports or series. Arthralgia prevalence in clinical trials ranged from 1 to 43%, and myalgia was reported in 2–20%. Arthritis was reported in 5/33 clinical trials, and vasculitis was reported in only 2. Case reports included development of IA, vasculitis, myositis, and lupus nephritis The single case of lupus nephritis reported occurred during ipilimumab treatment [19].

Le Burel, et al. screened a french, prospective, multicentre academic oncologic registry, the REISAMIC registry, and recruited cases of grade ≥ 2 irAEs occurring in ICPI-treated patients, in order to study the prevalence of irAEs in patients treated with anti-PD1/PDL1 [20]. Out of 908 patients treated with anti-PD1/PDL1 (together with an anti-CTLA-4 agent in 40 cases), 21 patients experienced systemic rheumatologic irAEs, including: immune thrombocytopenia (0.2%), SjS (0.3%), RA (0.2%), PMR (0.2%), PsA (0.2%), seronegative polyarthritis (0.7%) and sarcoidosis (0.2%). Patients with SjS or seronegative polyarthritis had more likely received combination therapy with ipilimumab (2.5% for both). Most irAEs were moderately severe (grade 2, 63%). The median time to onset was 57 days. The ICPI was withdrawn in 12 cases, 25 patients (83%) received GC, and five patients (17%) received immunosuppressant/immunomodulatory agents. The irAEs resolved fully or partially in 28 cases (93%).

The same authors in a further paper focused their attention, examining the same french registry, on the onset of a specific kind of ARD: connective tissue diseases (CTD) [21].

Of the 447 patients of the registry, authors evidenced four cases of CTD after therapy: 2 patients developed Sjogren's syndrome, 1 developed cryoglobulinemic vasculitis in a context of suspected Sjogren's disease and 1 patient had ANA + myositis. All patients had metastatic cancer, 3 were female and median age was 62 years. They had never manifested previously symptoms or signs of autoimmune pathology. The mean time interval between the first ICPI infusion and the first symptoms of CTD was 60 days. ICPI was discontinued for 3 patients and 2 of them were treated with glucocorticoids (GC).

Suarez-Almazor et al. in their review on irAEs in patients under immune cancer therapy reported 2 cases of onset of 2 different forms of arthritis in previously undiseased patients after starting checkpoint inhibition [22]. Patient 1, a 46 year old man affected by metastatic duodenal cancer developed oligoarthritis 9 weeks after initiation of anti-PD1 antibody combination with an anti T-cell immunoglobulin and mucin domain-containing protein antibody. The arthritis involved both

Table 2d
Papers analysed according to clinical question 4.

First Author	Year	Country	Study design (study name)	Patients included	Drug target
Le Burel S	2017	France	Observational retrospective study	908 patients (without ARD)	Anti-CTLA-4, Anti-PD-1
Suarez-Almazor ME	2017	USA	Case series	2 patients	Anti-PD-1
Calabrese C	2017	USA	Case series	15 patients (13 without, 2 with ARD)	Anti-CTLA-4, anti-PD-1, anti-PD-L1
Cappelli LC	2017	USA	Case series	13 patients	Anti-CTLA-4, anti-PD-1
Postow et al.	2018	USA	Review	NA	Anti-CTLA-4, anti-PD-1, anti-PD-L1

knees and left ankle; for what about laboratory tests ANA were weakly positive (ANA 1:80) and RF/anti-CCP were negative. This patient, who did not benefit of steroid injection, was treated with oral prednisone 40 mg daily with clinical efficacy and progressive slow tapering.

Patient 2, a 71-year old woman with NSCLC and no history of ARD, manifested onset of hands arthritis after 3 doses of nivolumab. RF was positive, in this case, while ANAs and anti-CCP were negative. She was treated, too, with oral prednisone; nivolumab was stopped, with clinical benefit. After few month, she was re-treated with nivolumab for a progression of the tumor and poliarthritis suddenly compared, so nivolumab was discontinued twice.

Moseley et al. in a recent retrospective case series studied the frequency of a particular type of irAE in patients treated with ICPIs: skeleton irAEs [23]. They analysed all clinical, laboratory and imaging data concerning patients referring to endocrinologic and rheumatologic centres with new fractures or resorptive lesions developed under treatment with ICPIs (anti-PD-1, anti-CTLA-4 or both) affected by different kind of tumors (MM, renal cell carcinoma and NSCLC). Six patients with skeletal irAEs were identified and studied. The average age of patients was 59.3 and 5 of them were male. Four patients were treated with anti-PD-1 and 2 with ipilimumab and nivolumab combination. Only one of the 6 patients had additional not musculoskeletal irAEs. Three patients had vertebral fractures and one of them had additional rib and pelvic fractures. No patient with fractures had osteoporosis by dual-energy X-ray absorptiometry (DXA) definition (i.e., all T-scores > -2.5). The other 3 patients manifested destructive or resorptive bone lesions; 2 of them had concomitant IA in separate joints that developed while receiving ICPI therapy. No patient in this series developed both skeletal phenomena. This kind of irAE could be explained by the fact that ICPIs promote a pro-inflammatory state with production of cytokines that influence bone metabolism with unbalanced skeletal remodeling state between osteoclasts bone-resorbing and osteoblasts bone-building [24,25].

They concluded that risk factors for skeleton irAEs should be carefully assessed, too, in these patients.

Summarizing, we can say that different kind of rheumatological manifestations can appear in patients under ICPI treatment; frequency is variable and arthralgias and mialgias seem the most frequent [10–12,16–25]. Severe events are rare and in most cases steroid therapy is resolutive [26].

Indeed, it seems that musculoskeletal adverse events are underrepresented because underestimated by most oncology publications that do not consider arthritis and other rheumatic irAEs as a severe event [27].

3.2. May ICPI affect the disease course of ARDs or, in other words, may ICPIs induce the onset of rheumatic irAEs in patients already affected by a ARD?

Johnson, et al. performed a retrospective analysis of patients with advanced melanoma and preexisting autoimmune disorders who received ipilimumab at 9 academic tertiary referral centers [28]. Of the 30 patients who received ipilimumab, 6 had RA, 5 had PsA, 2 had SLE, and 17 had other conditions. Thirteen patients (43%) were receiving immunosuppressive therapy at the time of initiation of ipilimumab therapy, most commonly low-dose prednisone or hydroxychloroquine. With ipilimumab treatment, 8 patients (27%) experienced exacerbations of their autoimmune condition necessitating systemic treatment; all were managed with GC. Conventional grade 3 to 5 irAEs occurred in 10 patients (33%) and were reversible with GC or with infliximab therapy in 2 cases. One patient with baseline psoriasis died of presumed immune-related colitis after a 1-week delay prior to reporting symptoms. Fifteen patients (50%) had neither autoimmune disease flares nor irAEs. Six patients experienced an objective response (20%), including 1 with a durable complete response.

In the case series reported by Calabrese et al. [17], previously described, there were 2 patients with a pre-established ARD, one affected by seropositive non-erosive RA and the other one by PsA. The patient with PsA experienced a psoriasis flare 2.8 weeks after starting nivolumab and apremilast was resumed with partial benefit. The patient affected by RA remained stable, without disease exacerbation, while on mantained Plaquenil.

Gutzmer et al. performed a retrospective multicentre study assessing patients undergoing anti-PD-1 therapy for MM with regard to flare of preexisting autoimmunity, development of additional irAEs as well as treatment response [29]. Preexisting pathologies included rheumatological disorders (RA, PMR, vasculitis, myositis, spondylarthritis, sarcoidosis), as well as other non-rheumatic autoimmune diseases (AID). Within 3–20 weeks on anti-PD-1 therapy, 8/19 patients with preexisting well controlled AID (42%) suffered from a flare of their AID. Rheumatological disorders flared in 55% (5/9 patients).

The FDA has evaluated a large cohort of patients with ARD and SMCLC treated with PD-L1 inhibitors including patients under steroid therapy at initial treatment [30]. Among them 9% had a worsening of their disease (grade 3 in 3% of cases) and only 17% experienced any irAE.

Abdel-Wahab, et al. conducted a systematic review of all reported cases describing the use of ICPIs in patients with cancer and preexisting AID to summarize the evidence on adverse events associated with ICPI therapy [31]. In 49 publications (39 case reports, 4 case series, 6 publications on 5 retrospective observational studies), 123 patients with pre-existing AIDs were identified, including 28 PsA, 20 RA, 5 sarcoidosis, 2 ankylosing spondylitis and 1 PMR; overall, 92 patients (75%) reported irAEs (any kind, including non-rheumatic ones). Fifty patients (41%) had exacerbation of the preexisting AID with recurrence or worsening of prior manifestations (with 1 reporting new disease features), 31 (25%) had de novo irAEs, and 11 (9%) had both. No differences in adverse events were observed in patients with active versus inactive disease. Patients receiving immunosuppressive therapy at initiation of ICPI therapy seemed to have fewer adverse events than those not receiving treatment. Because prospective observational studies were not included, incidence of irAEs could not be determined in this analysis.

Danlos et al. analysed the data from a prospective multicenter registry, in order to describe the safety and effectiveness of anti-PD-1 antibodies in patients with a pre-existing AID [32]. They identified 45 patients with a pre-existing autoimmune disease, including some affected by an ARD: 4 SjS, 2 RA, 1 PMR, 1 spondyloarthritis, 1 sarcoidosis, 1 polyarteritis nodosa, 1 chronic cutaneous lupus. At the time of ICPI initiation, 25 of the AID patients (55.6%) were symptomatic, 22 had stable disease and three had flares. Twenty of the 45 patients (44.4%) presented with an irAE or more, with 55% experiencing a disease flare. The most common was the exacerbation of psoriasis, observed in 4 of the 13 patients with pre-existing psoriasis, one of them developing psoriatic arthritis and pustular psoriasis. Excluding the patients with vitiligo,16 patients (51.6%) with a pre-existing AID did not develop an irAE after a median follow-up period of 5.1 months.

Menzies AM et al. conducted a further observational retrospective study on safety and efficacy of anti-PD-1 therapy in patients with advanced melanoma and preexisting ARD and/or major toxicity with ipilimumab (requiring systemic immunosuppression) [33]. 52 patients with a previous ARD were identified from a group of 119 patients treated with anti-PD-1 (109 pemrolizumab, 10 nivolumab), in a period from July 2012 and September 2015, in 13 different academic tertiary referral centers. The majority of patients had rheumatologic pathologies (27 total/52%: 13 RA, 3 sarcoidosis, 3 PMR, 2 SLE, 2 scleroderma, 2 psoriatic arthritis, 2 Sjogren disease). Other conditions were: dermatologic (6 psoriasis), gastrointestinal (3 Crohn's disease, 2 ulcerative colitis with colectomy) and neurologic conditions (2 Guillain Barrè, 1 chronic inflammatory demielinating polineuropathy, 1 myasthenia gravis) among others. At the beginning of anti-PD-1 therapy, 15 (29%) patients had active symptoms of autoimmunity, including 11 (21%)

with rheumatologic conditions (5 RA). Twenty (38%) patients were assuming immunosuppressive therapy, including GC (17%), immunosuppressants (10%) or both (10%). Globally, twenty (38%) patients had a flare of their underlying autoimmune disorder at a median of 38 days after the first dose of anti-PD-1 antibody. In general, they were represented by a recurrence or increased grade of a pre-existing symptom rather than a new clinical disease manifestation and occurred more often in patients with active disease (9/15, 60%) and in those who were taking immunosuppressants when starting anti-PD-1 treatment (10/20, 50%). Particularly, flares occurred in 14/27 (52%) patients with rheumatologic disorders. Most flares of autoimmune disorders were mild. To note, no patients with gastrointestinal or neurological or respiratory disorders had a flare. Patients were managed with oral GC and immunesuppressive therapy. For what about ICPIs, while 8 patients temporarily interrupted therapy, only 2 (10% of flares, 4% of total treated) permanently discontinued therapy because of the reactivation of autoimmune disorders.

Conventional irAEs occurred in 15 (29%) patients; most irAEs (8/15, 53%) settled with symptomatic/conservative management only. This data were similar to the ones evidenced in clinical trial populations. There were no treatment related deaths. The response rate to the ICPI was 33% and it was the same comparing patients with and without flares. The response rate was lower in patients on immunesuppressants at the beginning of therapy.

Authors, in this first study analyzing this subgroup of patients, concluded that, taken together their data, anti-PD-1 could be administered safely and give clinical benefits also in melanoma patients with ARD, but a close and interdisciplinary monitoring is necessary.

Leonardi et al. conducted another multi-institutional retrospective study to evaluate safety of anti-PD-1 in patients with another type of cancer, non-small cell lung cancer (NSCLC), and a preexisting autoimmune disease (AID) [34]. They identified 56 patients with NSCLC and an AID treated with anti-PD-1; when starting therapy 18% had active AID and 20% were assuming immunosuppressants. Globally, 55% of patients developed a flare and/or an irAE; 3 patients developed both an AID flare and a separate irAE. Particularly, flares of the AID occurred in 13 patients (23% of the cohort) and 4 of them were treated with systemic GC. Rheumatologic patients had a higher proportion of flares compared with other ones (40% vs 10%); among the 25 patients with rheumatic diseases, 8 had active symptoms when they started anti-PD-1 therapy and 4 were assuming immunosuppressive drugs. Two patients with psoriasis experienced both worsening of the cutaneous disease and grade 2 arthralgias. One patient with seronegative arthritis developed grade 3 arthralgias and grade 2 nephritis that determined nivolumab discontinuation.

None of the patients required permanent discontinuation of anti-PD-1 because of an AID exacerbation. Therapy for cancer was discontinued globally in 8 patients (14%) because of irAEs. Response rate was 22% in this cohort and disease control rate was 53%. Authors did not find association between the use of immunomodulatory treatment at the time of PD-(L)1 inhibitor start and response to ICPI and no association between the development of AID flare and response to immunotherapy.

An interesting case report described by Maul et al. in 2016 documented the successful treatment of a patient with a severe ARD and MM with anti-PD-1 antibody therapy [35]. Particularly, the patient was a 69-year old man with a history of Churgh-Strauss syndrome with pulmonary and cardiac involvement from 2007 who was assuming prednisolone 3 mg daily since 2012, previously treated with higher doses of steroids and azathioprine. He had been diagnosed a nodular metastatic melanoma in 2007 (AJCC stage IV) and had been treated with dacarbazine, with progression of the disease; after, he had started in 2013 ipilimumab but after 3 infusions he had presented an immune related colitis that had resolved after GC treatment. For a progression of cancer, in December 2014 he began a cycle of therapy with pemrolizumab, at a dose of 2 mg/kg every 3 weeks, after an intensive discussion of the specialists because of the high risk for both colitis and vasculitis. The treatment was well tolerated by the patient, with no exacerbation of the ARD, no colitis, and cancer remission. This is another case showing that pemrolizumab might be used in patients with a pre-existing ARD, even a severe one, with careful monitoring.

To conclude, ICPIs can influence the course of a rheumatic pre-existing ARD; rheumatic irAEs are, often, mild and can be managed with steroids or immunosuppressive therapy. This must be considered and carefully evaluated before starting ICPI and during treatment.

3.3. How to treat the patient who develops rheumatic irAEs or an ARD following ICPI treatment? Has ICPI therapy to be discontinued?

To date, there are no specific guidelines in the treatment of irAEs or ARDs flares in patients following ICPI treatment and it is difficult for the community of onchologist and rheumatologists to manage them and to decide if and when continue, or not, ICPI therapy.

Naidoo J. et al., after an examination of all literature data about arthralgias and IA in patients treated with ICPIs, proposed a management algorithm for immune-related arthritis [36]. They asserted that patients with suspected IA, had to be assessed by physicians for joint pain and swelling, morning stiffness and limited range of motion, should perform laboratory test, including a panel of inflammatory and serologic markers, and should undergo to radiological imaging of affected joints to identify active and erosive disease. Authors also stated that rheumatological referral should be considered to make an accurate diagnosis and to manage patients with moderate-severe symptoms or symptoms lasting > 4 weeks or requiring > 20 mg of prednisone per day that cannot be tapered to < 10 mg in 4 weeks. To treat IA they suggested to start, in grade 1 cases, with non steroidal anti-inflammatory drugs (NSAIDs) and intra-articolar GC (large joints, < 3 joints affected) and, if NSAIDs uneffective, with prednisone 10–20 mg daily x 4 weeks; immunotherapy should be continued. In grade 2 cases, they suggested to consider to hold immunotherapy, prescribe prednisone 20 mg daily x 4–6 weeks and increase to 1 mg/kg/day or equivalent; if there was no response in 4–6 weeks they suggested to escalate to grade 3. In this case, immunotherapy should be stopped and arthritis should be managed with prednisone 1 mg/kg/day x 4 weeks or until symptoms last and additional immunosuppressant should be considered (eg. TNF-inhibition, Methotrexate, leflunomide, sulfasalazine).

In the series of 10 patients who developed AR or PMR reported by Belkhir [12], immunosuppressants/immunomodulators were needed for 3 patients with RA (hydroxychloroquine for two and methotrexate for one), while the others 3 patients with RA received only GC or NSAIDs. The 4 patients with PMR responded to GC. The ICPI therapy was continued for all patients but one until cancer progression. Nivolumab was stopped in only one patient with RA who showed no improvement with GC and, because cancer was stable, methotrexate was introduced.

In the series reported by Calabrese et al. [17] immunotherapy was maintained in the majority of the patients developing irAEs. Treatment of rheumatic irAEs was done with corticosteroid, TNF-alfa inhibitors, intravenous immunoglobulin or hydroxychloroquine.

In the retrospective analysis reported by Gutzmer et al. [29], flares in patients with pre-existing ARD treated with anti-PD-1 therapy, were controlled by immunosuppressive and symptomatic drugs (including prednisone, methotrexate, sulfasalazine, TNF inhibitors) and did not require termination of anti-PD-1 therapy.

In the systematic review conducted by Abdel-Wahab, et al. [31], most flares and irAEs were managed with steroids; 16% required other immunosuppressive therapies (methotrexate, hydroxychloroquine, azathioprine, infliximab, adalimumab, secukinumab, apremilast, or rituximab). Adverse events improved in more than half of patients without discontinuation of ICPI therapy. However, 21 of the 123 patients (17.1%) discontinued ICPI therapy permanently, because of an adverse event, and 3 patients died.

In the analysis of the data from a prospective multicenter registry reported by Danlos et al. [32], anti-PD-1 antibody infusions were maintained in 15 (75%) of the 20 cases presenting an irAE, and 12 patients received specific treatment for the irAE.

In the study conducted by Menzies et al. [33], most patients flares were mild and were managed with oral GC and immunosuppressive agents. Eight patients, who developed a flare of the pre-existing ARD, temporarily interrupted therapy with anti-PD-1; only 2 (10% of flares, 4% of total treated) permanently discontinued therapy because of the reactivation of autoimmune disorders.

In the retrospective analysis reported by Leonardi et al. [34] flares of the AID, including ARD, were managed with NSAIDs and analgesics in most cases. Particularly, concerning rheumatologic patients, 1 SLE patient required use of topical corticosteroids and prednisone for rash; 1 RA patient required an intra-articular injection of steroids while another one NSAIDs and oral prednisone, 1 RA/PMR patient required a steroid injection and oral prednisone, 1 RA patient started hydroxicloroquine. Other patients who flared were managed with topical steroids, NSAIDs and analgesics. Noone had to discontinue ICPI therapy permanently and was discontinued temporarily in 2 patients, one with SLE and one with RA.

Interestingly, Esfahani reported on a patient affected by metastatic colon cancer who had been treated with third-line pembrolizumab after disease progression [37]. This patient had a severe adverse reaction after the third cycle of pembrolizumab, with a psoriatic rash involving > 75% of the body surface area, associated with intense arthralgias and pruritus. He was given once-weekly subcutaneous administration of 150 mg of secukinumab, a human monoclonal antibody that selectively binds to circulating interleukin-17A cytokine and inhibits its interaction with the interleukin-17 receptor. After secukinumab therapy, he experienced complete resolution of the skin psoriasis, but there was cancer progression during continuation treatment with both pembrolizumab and secukinumab, suggesting that interleukin-17 may play a role in the antitumor effects of checkpoint inhibitors such as pembrolizumab.

Spain et al. [26], in their review on the management of different toxicities in patients treated with ICPIs, suggested the following indications for rheumatological irAEs: for mild symptoms, analgesia with paracetamol or NSAIDs, for moderate symptoms low-dose prednisolone, for severe symptoms higher dose GC (prednisolone 1 mg/kg) and early rheumatological consultation. It is important to underline, as the authors do, that treatment with GC and other immunosuppressive drugs for prolonged periods may be associated with short-term side effects such as opportunistic infection, insomnia, mood disturbance, gastritis, diabetes and hypertension in addition to long-term side effects such as osteoporosis. They recommend prophylaxis against *Pneumocystis jirovecii* pneumonia in patients who receive > 25 mg prednisolone per day for more than four weeks. They also suggest occasional blood sugar monitoring to screen for diabetes and optimisation of vitamin D levels.

There are no conclusive data about management of irAEs and necessity to discontinue ICPI or not; different cases have to be individually analysed and evaluated according to clinical data.

3.4. Do predictive factors of increased risk of rheumatological irAEs exist? (Autoantibodies may predict the occurrence of a ARD in a previously undiseased patient undergoing ICPI treatment)

The reason for the occurrence of rheumatological irAEs only in certain patients is unknown and this is not clear for all types of adverse manifestations. For this reason, some studies are investigating whether factors, such as genetics ones or host microbiota are implicated in the pathogenesis, but, additional research is needed [38].

Few evidences have emerged in these articles about autoantibodies positivity and the occurrence of rheumatic irAEs.

In the study conducted by Le Burel et al. [21] examining patients from REISAMIC registry, authors evidenced that 3 of the 4 patients, who developed a ARD after ICPI therapy, were positive for anti-nuclear antibodies (ANA) before treatment; 2 of them had anti-SSA (Ro) and anti-SSB (La) without signs or symptoms of ARD. Could be ANA a test to perform, before starting immune therapy, to stratify patients at risk? The authors did not discuss this issue, but they underlined the importance to screen asymptomatic patients for risk of irAEs.

In the review by Suarez et al. [22], ANA and anti-cyclic citrullinated peptide antibodies (anti-CCP) were negative in the 2 patients who developed arthritis after therapy with ICPIs, while rheumatoid factor (RF) was positive in the second patient.

In the review by Calabrese et al. [17], autoimmune testing showed the presence of various autoantibodies, including ANA, anti-double stranded DNA antibodies (anti-dsDNA), RF, anti-SSA (Ro), only in some cases.

Finally, in the report from Cappelli et al. [9] on 13 patients treated with ipilimumab and/or nivolumab for NSCLC, MM or renal cell carcinoma, who developed new rheumatological symptoms, three of the sicca syndrome patients had ANA, 1 patient had anti-SSB (La) antibodies and 1 patient was RF-positive; a patient had anti-EJ antibodies (one of the anti-synthetase antibodies), without Raynaud's phenomenon, cutaneous rash or evidence of myositis.

To date, predictive factors of increased risk of rheumatological irAEs have not been addressed; autoantibody profile and disease activity in patients who are affected by a ARD can be useful.

4. Discussion

Immunotherapy has improved and enriched therapeutic armamentary for cancer: lot of studies have demonstrated that it is safer than chemotherapy. However, immunotherapy for cancer can enhance the development of different irAEs, including rheumatological ones, that require multidisciplinary management; this is related to the role of the immune checkpoints in balancing immunologic homeostasis.

Patients affected by ARDs represent a special population not only because, based on the assumption that autoimmune toxicity could be exacerbated, they usually are excluded from clinical trials on ICPI, but also because, while ICPI therapy enhances T-cell immune response, drugs treating ARDs inhibit T-cell immune response.

In this paper, we aimed to analyze the existing scientific literature dealing with the complex interrelationship between ICPI treatment and ARDs, in order to give an answer to various clinical questions.

Literature data show that ICPI therapy may induce several rheumatic irAES and even rheumatic diseases in previously undiseased patients. Indeed, it seems that musculoskeletal adverse events are underrepresented because most oncology publication report grade 3 and higher adverse events, and arthritis is not considered as a severe event. Studies designed to assess whether predictive factors of increased risk of rheumatic irAEs exist have not been performed, even if there is some evidence that autoantibody testing in patients not affected by ARD may be helpful before starting ICPI therapy.

The spectrum of rheumatic irAEs in previously undiseased patients encompass arthralgias, whose prevalence ranges from 1 to 43% in reported studies, myalgias (2–20%), arthritis, seropositive RA, myositis, PMR, sicca symptoms, Sjogren's syndrome, skeleton irAEs (fractures and resorptive lesions), and less commonly vasculitis, cryoglobulinemic vasculitis and lupus nephritis. Time of onset of these manifestations can vary from a week to several months after ICPI initiation. When such irAEs develop, ICPI therapy can be continued in those patients without severe toxicity, and rheumatic irAEs can disappear spontaneously despite ICPI continuation, but usually they tend to persist and require treatment. The different role of CTLA-4, that inhibits immune response in a proximal step compared to PD-1, can explain the different toxicity of drugs that inhibit one or another. In fact, ipilimumab has generally shown more toxic effects than anti PD-1. In addition, the fact that the 10 cases of rheumatological irAEs, reported by Belkhir, occurred only after anti-PD-1 and not anti-CTLA-4 antibody treatment (except one

patient who received both during four cycles) suggests a contrast between irAEs occurring after blockade with CTLA-4 (colitis, endocrine disorders, skin rashes) and PD-1/PD-L1 (non-specific arthritis, sicca syndrome, RA, PMR, and other connective tissue diseases) [12].

More often, ICPI therapy may induce disease exacerbation in patients already affected by ARD. This can occur in about 40–50% of cases. Generally, rheumatic irAEs appear in the first weeks or few months after beginning of therapy but they can develop in every moment, also after discontinuation of therapy. The most frequent event seems to be psoriasis exacerbation, but exacerbation of RA, PsA, SLE, scleroderma, chronic cutaneous lupus, vasculitis, Sjogren's syndrome, ankylosing spondylitis, myositis, sarcoidosis, have all been reported. Rheumatologic patients seem to have a higher proportion of flares compared with patients affected by non-rheumatologic autoimmune diseases. Overall, no differences in adverse events seem to exist in patients with active versus inactive disease, whereas patients receiving immunosuppressive therapy at initiation of ICPI therapy seem to have fewer irAEs than those not receiving treatment.

These rheumatic irAEs are usually mild and can benefit from treatment with NSAIDs, systemic GC, or immunosuppressant drugs such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and biological DMARDs. Treatment algorithms that take into account the severity of irAEs have been proposed. In most cases, patients do not require permanent discontinuation of ICPI following ARD exacerbation, because these irAEs are usually mild and can be treated by GC or immunosuppressants. Indeed, flares and irAEs in patients with ARDs who are receiving ICPIs can often be managed without discontinuing therapy, although some events may be severe and fatal. The combined expertise of oncologists and rheumatologists is crucial for successful management of these patients and prescription of anti-tumor necrosis factor antibodies or other DMARDs may be possible, if needed, with this multidisciplinary expertise. Even if onchologists and rheumatologists wonder if using steroid and immunesuppressive therapy to treat irAEs may impact on the efficacy and safety of ICPIs, data from observational studies and case reports seems to indicate the relative safety of these treatments. However, in some cases ICPIs had to be definitively interrupted.

According to some Authors the use of PD-1/PD-L1 inhibitors in patients with NSCLC and active autoimmune disease requiring systemic treatment, is not recommended [39].

Other Authors, given that patients requiring regular high-dose GC or immunosuppression respond less frequently to immunotherapy, suggest that cancer immunotherapy should only be considered in patients in stable remission not requiring immunosuppressive treatment, trying to reduce the GC dose to < 10 mg daily prednisone equivalent before starting anti-PD-1/PD-l1 therapy [33].

In a recent review article on this item, Postow et al. [38] suggest, according to emerging data, that patients with an underlying autoimmune disorder should be considered for treatment with immune checkpoint blockade if they have a life-threatening cancer and that the risks and benefits of such therapy should be weighed in consultation with appropriate subspecialists.

However, in the context of an otherwise fatal illness such as cancer, there may be greater willingness to accept the risk of toxicity, particularly in the absence of alternative effective therapies. Until further data are available, particularly from real-world clinical settings, close monitoring in conjunction with appropriate specialist care it is recommended to ensure early identification and effective management of irAEs.

Finally, onchologists and rheumatologists wonder if using glucocorticoids and immunesuppressive therapy to treat irAEs may impact on the efficacy and safety of ICPIs. There are not studies that have proven the reality of this theoretical risk; data from retrospective studies have globally evidenced that this does not happen, but more studies are needed to address this issue and to evaluate single different drugs profiles [37,40]. However, adding immunosuppressive drugs to ICPIs, increases other risks that have to be considered. For example longterm GC, frequently needed to control adverse events, can provoke osteoporosis, glaucoma, cushing syndrome, debilitating proximal muscle weakness and opportunistic infections such as Aspergillus pneumonitis, cytomegalovirus hepatitis and pneumocystis pneumonia [41,42]. Given this potential risk of opportunistic infection, when patients require 20 mg of prednisone daily or the equivalent for at least 4 weeks, *Pneumocystis jirovecii* prophylaxis with trimethoprim, atovaquone, or pentamidine should be considered [36].

5. Conclusion

According to emerging data, globally, rheumatological irAEs are not infrequent in patients treated with ICPIs, but they are often mild and reversible.

In patients affected by ARDs, ICPI treatment should be considered, in case of life-threatening cancer, but with close monitoring and interdisciplinary follow up in order to have best management.

Before starting ICPI therapy in ARD patients a careful assessment of disease activity, risk factors for skeletal irAEs, autoantibody profile, and current treatment is of outstanding importance [43,44].

However, further data are necessary to implement our knowledge about this item. Different questions remain not well addressed or not addressed at all: which are the pathogenetic causes of irAEs? what is the frequency and type of controls in ARD patients under ICPI therapy? Do the presence of ARDs have some influence on ICPI safety and efficacy? Do Disease Modifying Antirheumatic Drugs and GC impact on the efficacy (and safety) of ICPI? Prospective longitudinal studies are needed to answer these questions, to establish the incidence of irAEs in this special population (ARD patients) and to evaluate risk-benefit ratios and patient profiles to stratify them

Conflict of interests

Authors declare no conflict of interest.

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