Rheumatic Complications of Immune Checkpoint Inhibitors

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KEYWORDS

• Immune-related adverse events • Immune checkpoint inhibitors • Cancer
• Rheumatoid arthritis • Polymyalgia rheumatica • Myositis
• Disease-modifying antirheumatic drugs

KEY POINTS

- Immune checkpoint inhibitors can lead to autoimmune side effects called immune-related adverse events, which can mimic rheumatic diseases, such as rheumatoid arthritis, polymyalgia rheumatic, and polymyositis.
- Immune-related adverse events are common and can range in severity from asymptomatic to lethal.
- Due to the potential for high morbidity and mortality, prompt recognition of these events is important.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have dramatically changed how cancer has been treated in the past decade. These agents have been shown to provide significant survival benefits, especially after more traditional chemotherapies have failed. Immune checkpoint blockade allows T cells to overcome physiologic inhibitory mechanisms and mount an antitumor response[1–3] (**Fig. 1**). Although there are several checkpoint inhibitors under study and in production, there are 3 main classes of ICIs at this time, those targeting cytotoxic T-lymphocyte–associated protein-4 (CTLA-4), programmed cell death protein 1 (PD-1) or its ligand, and programmed death ligand 1 (PD-L1).

ICIs have been approved for the treatment of many malignancies, including melanoma, non–small cell lung cancer, renal cell carcinoma, and urothelial tumors (**Table 1**). They also have been approved for the treatment of tumors with mismatch repair (MMR) defects and/or a high mutational burden, regardless of the organ involved.[4,5] These tumors produce high levels of neoantigens, resulting in increased

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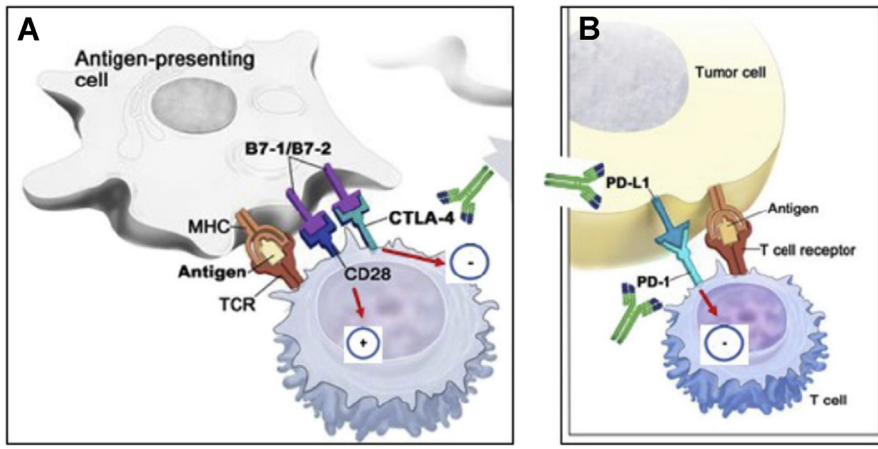

Fig. 1. Mechanism of action of ICIs.(*A*) Within the lymph node, an antigen is presented to a naive T cell receptor (TCR). CD28 on the T-cell binding to B7 provides the second signal needed to fully activate the T cell. CTLA-4 is a negative regulator that competes with CD28 to bind to B7 to turn the T cell off preventing overactivation. Antibodies to CTLA-4 block this inhibitory step, allowing for continued T-cell activation. (*B*) A cytotoxic T cell binds to a cancer cell's surface antigen via the TCR without the need for a second signal. PD-1 binding to PD-L1 on the target cell sends an inhibitory signal to the T cell to turn the cell off. Antibodies that block either PD-1 or PD-L1 block this inhibition. (For the National Cancer Institute Q 2019. *Adapted from*: Terese Winslow LLC, with permission. U.S. Govt, has certain rights.)

immunogenicity and sensitivity to ICIs. ICIs can be used alone, in combination, and/or in conjunction with conventional chemotherapy, radiotherapy, or surgery. Although they generally are used in patients with metastatic (stage IV) cancer, they increasingly are used as adjuvant therapy in patients with locally advanced cancers (stage III).

Although ICIs can effectively treat some cancers, ICI-induced T-cell activation can lead to autoimmune side effects, termed *immune-related adverse events* (*irAEs*).[6] The mechanisms underlying irAEs are not well understood, but activated cytotoxic T cells seem to play a direct role in some irAEs, such as myositis, whereas other irAEs appear to be antibody mediated, such as bullous pemphigoid.[6]

IrAEs occur in 80% to 90% of patients and can affect multiple organ systems in the body, including the skin, gastrointestinal (GI) tract, lungs, endocrine organs, and heart (**Table 2**). Approximately 5% of patients develop rheumatic complications, such as inflammatory arthritis.[6,7] Tumor type does not significantly influence which organs are targeted by irAE, but the specific ICI treatment does. For example, thyroid dysfunction and arthralgias are more common with PD-1 and PD-L1 blockade, whereas colitis and hypophysitis are more common with CTLA-4 blockade. The frequency and severity of irAEs are highest with combination therapy (anti–CTLA-4 plus anti–PD-1).[8] Within organ systems, irAE manifestations can vary from patient to patient. For example, skin involvement can manifest as vitiligo, lichenoid reactions, psoriasis, bullous pemphigoid, or Stevens-Johnson syndrome. Endocrine manifestations also are varied, including thyroiditis, leading to both hyperthyroidism and hypothyroidism, hypophysitis, type 1 diabetes mellitus, or adrenal insufficiency. IrAE severity is graded using the Common Terminology Criteria for Adverse Events (CTCAE) system and ranges from mild (grade 1), to moderate (grade 2), to severe and generally requiring hospitalization (grade 3), to life-threatening (grade 4), and to death (grade 5).[9] In the GI tract, for

Table 1
Food and Drug Administration–approved indications for immune checkpoint inhibitors

	Brand Name	Target	Food and Drug Administration Approval Year	Cancers Approved for Drug Use
Ipilimumab	Yervoy	CTLA-4	2011	Melanoma, renal cell carcinoma, colorectal cancer
Nivolumab	Opdivo	PD-1	2014	Melanoma, non–small cell lung cancer, small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell cancer, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal cancer
Pembrolizumab	Keytruda	PD-1	2014	Melanoma, non–small cell lung cancer, small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, large B-cell lymphoma, gastric cancer, esophageal cancer, cervical cancer, Merkel cell carcinoma, head and neck squamous cell cancer, urothelial carcinoma, bladder cancer, colorectal cancer, hepatocellular carcinoma, advanced MSI-H/dMMR
Cemiplimab	Libtayo	PD-1	2018	Cutaneous squamous cell carcinoma
Avelumab	Bavencio	PD-L1	2017	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Atezolizumab	Tecentriq	PD-L1	2016	Urothelial carcinoma, non–small -cell lung cancer, small cell lung cancer, bladder cancer, breast cancer, hepatocellular carcinoma
Durvalumab	Imfinzi	PL-LI	2017	Urothelial carcinoma, non–small lung cancer, small cell lung cancer

Abbreviations: MSI-H, microsatellite instability–high; dMMR, deficient MMR.

example, patients can have an increased number of daily bowel movements (grade 1) or frank colitis with perforation (grade 4 or 5). At present, biomarkers are lacking to predict the type and severity of irAE that an individual patient experiences, so close monitoring is of the essence. A majority of irAEs typically occur in the first 3 months after ICI initiation; however, irAEs can occur much earlier, within days of ICI initiation, to months after ICI discontinuation.[10,11] Fatal irAEs tend to occur soon after ICI initiation but they also can have a delayed or insidious onset.[12]

Although irAEs sometimes can result in significant morbidity or even mortality, they are associated with better cancer responses to ICI.[13] Early studies showed that melanoma patients who developed vitiligo after anti–CTLA-4 or anti–PD-1 had a

Table 2
Medications used in the management of immune-related adverse events

Drug (Target)	Onset of Action	Toxicity	Monitoring
NSAIDS	<1 d	GI Renal HTN Hepatitis	Baseline creatinine, Periodic creatinine for chronic use
Corticosteroids	<1 d	Infection Weight gain Osteoporosis Diabetes Hypertension Osteonecrosis Emotional lability	Baseline bone density, q2–3 y for chronic use BMP glucose or HgA1c for chronic use
Hydroxychloroquine	2–3 mo	Retinal pigmentation Neuropathy Myopathy, cardiomyopathy Skin pigmentation	Yearly eye examination
Sulfasalazine	2–3 mo	Sulfa allergy Headache GI Hematological Proteinuria Liver test abnormality	CBC, LFT, U/A 1 mo after initiation, then every 3–4 mo
Methotrexate	2–3 mo	Infection Mucosal ulcers Cytopenias Liver test abnormality, cirrhosis Pulmonary fibrosis	CBC, LFTs monthly × 3, then every 3–4 mo
Mycophenolate mofetil	1–3 mo	Infection GI Cytopenias	CBC, LFTs monthly × 3, then every 3–4 mo
TNFis[a]	<1 mo	Infection Multiple sclerosis Neuropathy Drug-induced lupus Psoriasis Rash	Baseline CBC, CMP, hepatitis B sAg, hepatitis B cAb, Quantiferon TBG CBC, LFTs 3 mo after initiation
IL-6R inhibitors [b]	<1 mo	Infection Cytopenias Liver test abnormalities Hyperlipidemia Intestinal perforation	CBC, LFTs monthly × 3, then every 3–4 mo Baseline lipids, retest 8 wk later
IVIG	<1 mo	Fluid overload Aseptic meningitis	IgA (evaluate for deficiency)
Rituximab (anti-CD20 B cell)	2–3 mo	Infection Infusion reactions Neutropenia Hypogammaglobulinemia PML	CBC 2–4 mo after infusion, CBC and quantitative immunoglobulins before each cycle

Abbreviations: BMP, basic metabolic panel; cAb, core antibody; CBC, complete blood count; HgA1c, Hemoglobin A1c; IgA, Immunoglobulin A; IVIG, Intravenous immunoglobulin; LFT, liver function test; QuantiFERON TB-Gold, TB Interferon-Gamma Release Assay; sAg, surface antigen; U/A, urinanalysis.

[a] Infliximab, adalimumab, certolizumab, golimumab, etanercept.

[b] Tocilizumab, sarilumab.

significant survival benefit.[14,15] Later studies have shown a similar benefit from irAEs in general, especially in patients treated with anti–PD-1 or anti–PD-L1 agents.[13,16]

Because controlled trials to guide irAE management still are lacking, guidelines borrow from the literature on de novo autoimmune diseases, such as rheumatoid arthritis or inflammatory bowel disease, and rely heavily on corticosteroids and tumor necrosis factor inhibitors (TNFis), in refractory cases. Abatacept (CTLA-4 Ig), a CTLA-4 agonist used for the treatment of rheumatoid arthritis, generally is avoided because its mode of action is directly contrary to that of the ICI ipilimumab (anti–CTLA-4), raising concerns that it would abrogate the antitumor effects of ICI. It has been used, however, in a case of refractory and life-threatening ICI myocarditis.[17]

In this article, the authors review rheumatic irAEs that may be encountered in general medicine practice. A guiding principle is that early recognition and treatment of irAEs are important in order to minimize morbidity and mortality.

IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH PREEXISTING AUTOIMMUNE DISEASE

There have been several retrospective studies evaluating the outcomes of ICI in patients with preexisting autoimmune disease. In general, approximately 75% of autoimmune disease patients have an irAE after ICI treatment, half an exacerbation of their autoimmune disease, one-third a de novo irAE, and some both. IrAE rates are lower in patients on immunosuppression at the time of ICI initiation, but cancer responses to the ICI also are lower in those patients.[18] Therefore, the authors recommend discontinuing or lowering the dose of immunosuppression prior to ICI initiation if the autoimmune disease itself is not life-threatening.

APPROACH TO THE PATIENT WITH MUSCULOSKELETAL COMPLAINTS AFTER IMMUNE CHECKPOINT INHIBITORS

When patients present with musculoskeletal pain after ICI treatment, the first step is to determine which organ is affected: joint, tendon, enthesis (the site where tendons or ligaments insert on bone), muscle, or nerve. If the joints are affected, then the number of joints and their distribution and symmetry can help characterize the arthritis phenotype as rheumatoid arthritis-like, spondyloarthropathy-like, polymyalgia rheumatica (PMR)–like, or a monoarthritis that could represent activated osteoarthritis (Fig. 2). Some patients have joint pain without joint swelling, characterized as arthralgia.

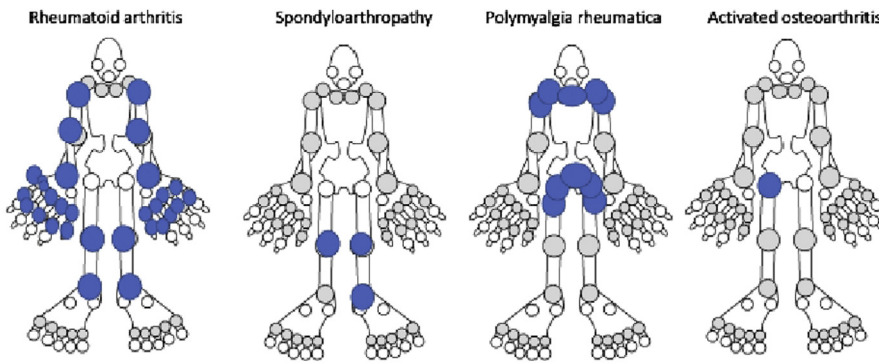

Fig. 2. Examples of ICI-associated musculoskeletal phenotypes (blue dots indicate tender and/or swollen joints). (Figure reproduced and modified with permission from CaRE Arthritis.)

It also is important to document the severity of irAE symptoms because this guides the choice of therapy and whether the ICI should be held or discontinued. In addition to assigning an irAE grade (arthritis generally is graded 1–3), some kind of numerical disease activity score is helpful to monitor patients' response to therapy. The simplest is to document the patients' global assessment of arthritis activity on a visual analog scale (VAS) from 0 to 10 as well as the provider's VAS 0 to 10. The duration of morning stiffness (in minutes or hours) also is a useful marker of disease activity. In patients with frank arthritis, the number of tender and swollen joints also should be documented. The clinical disease activity index (CDAI)[19] is the sum of the tender and swollen joints (28-joint count) and patient and physician arthritis activity scores on a VAS: 0 to 10 is mild disease activity, 11 to 22 moderate, and greater than 22 high disease activity. The CDA provides a more nuanced assessment of arthritis disease activity than irAE grade and can be useful to track response to therapy from visit to visit.[19]

A targeted rheumatology review of systems can help screen for new conditions associated with musculoskeletal pain. The presence of psoriasis may point to a spondyloarthropathy, whereas dryness of the eyes or mouth, oral or nasal ulcers, photosensitivity, or Raynaud phenomenon might suggest a connective tissue disease, like sicca syndrome (similar to Sjögren disease) or lupus. Lupus-like conditions, however, are uncommon in the context of ICI treatment. A personal or family history of autoimmunity, such as rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease, or uveitis, may point to one of those conditions being induced or unmasked by ICI.

Radiographic imaging is important especially in patients presenting with only 1 or 2 painful joints, in order to rule out underlying osteoarthritis or metastatic disease. Avascular necrosis also should be considered, especially in patients who have received high doses of corticosteroids for treatment of nonmusculoskeletal irAEs. Because back pain is uncommon in ICI arthritis, patients presenting with new and significant primarily axial complaints always should undergo imaging, often with magnetic resonance imaging (MRI), to rule out metastasis and/or pathologic fracture. The authors recommend hand radiographs to rule out erosions, particularly in patients with an rheumatoid arthrisit–like presentation, and of the knees if they are disproportionately affected. Normal radiographs, however, do not rule out the presence of an inflammatory arthropathy. Ultrasound of the joints can be used to identify synovitis when the physical examination is hard to interpret or to localize effusions for the purpose of joint aspiration.

Joint aspiration provides an opportunity to assess the degree of joint inflammation, rule out ICI-unrelated crystal disease, rule out infection (particularly if only 1 joint is affected), and inject with corticosteroids, if clinically indicated. The authors recommend referral to a rheumatologist if the patient has significant arthritis, for early consideration of steroid-sparing agents. Similarly, patients who are unable to taper corticosteroids within a month of treatment, even to a low dose (<10-mg prednisone equivalent), benefit from rheumatology consultation in order to consider additional therapies.

TREATMENT OVERVIEW

In general, the treatment of rheumatic irAEs is tailored to the organ system affected and the severity/grade of the irAE. Specific irAE treatment is outlined later, but some general principals follow. Grade 1 irAEs generally can be managed with symptom-directed therapies, such as analgesics or nonsteroidal anti-inflammatory drugs (NSAIDS), local injections if indicated, and, if necessary, low-dose prednisone,

generally 10 mg or less. ICIs can be continued in patients with grade 1 irAE. For grade 2 irAE, higher doses of corticosteroids generally are required, and ICIs may be temporarily held. There is a low threshold for initiating steroid-sparing agents for rheumatic irAEs because they often persist, and patients can experience side effects related to long-term use of corticosteroids. Some of the disease-modifying antirheumatic drugs (DMARDs) that are used to manage irAEs are listed in **Table 3**. Mild but slow-acting steroid-sparing DMARDs include hydroxychloroquine and sulfasalazine, whereas more potent slow-acting agents include methotrexate and mycophenolate mofetil. In patients with grade 3 irAEs or patients with grade 2 irAEs who are unable to taper corticosteroids, biologic DMARDs are an attractive choice because of their relatively rapid onset of action. TNFis, in particular infliximab, now are standard of care for the management of steroid refractory ICI-induced colitis, and their early introduction in that setting is associated with a faster resolution of symptoms and a reduced risk of infection compared with high-dose corticosteroids alone.[20–22] The use of TNFis for the management of ICI arthritis has been described in several cohorts,[23,24] but large published series documenting their overall effectiveness and safety in comparison to other approaches are lacking.

The use of immunosuppressive agents to control irAEs might be presumed to counteract the beneficial effects of ICI treatment on cancers but this has been difficult to demonstrate, perhaps because irAEs themselves are associated with improved survival.[13,15,16] One retrospective study of patients treated for ICI-induced hypophysitis demonstrated a marked reduction in survival in those treated with high-dose compared with low-dose corticosteroids.[25] In cases of TNFi, retrospective studies have produced conflicting results in regard to their impact on survival.[22,26] Although patients with ICI-induced colitis often require only a single dose of infliximab, patients with ICI arthritis tend to have persistent symptoms over months,[27] so the long-term safety of these agents is important, particularly in this setting. Preclinical studies suggest that the short-term use of TNFi may, if anything, be beneficial in combating tumors.[28]

Rheumatic Immune-related Adverse Events

Inflammatory arthritis

Joint pains (arthralgia) occur commonly in ICI-treated patients. A meta-analysis of clinical trials estimated the incidence (95% CI) of arthralgia to be 5% (3%–9%) with anti–CTLA-4, 8% (7%–11%) with anti–PD-(L)1, and 11% with the combination.[8] A 3-way head to head ICI trial also showed that joint pain is most frequent in patients getting combination therapy and least frequent with anti–CTLA-4.[1] Inflammatory arthritis (joint pain accompanied by joint swelling) is less common than arthralgia; however, estimates are hard to come by because joint swelling rarely has been documented in the context of these clinical trials. In 1 large prospective ICI cancer cohort, 3.8% of patients were referred to a rheumatologist for inflammatory arthritis.[29] This also may be an underestimate, however, because arthritis symptoms sometimes are ignored, especially if a patient is experiencing a potentially life-threatening irAE, such as colitis. In addition, treatment of nonarticular irAEs with corticosteroids or TNFis can treat the arthritis as well, and the arthritis then may go undetected.

ICI arthritis typically occurs in the first several months after ICI initiation but can occur more than a year after ICI initiation. In 1 cohort of 30 ICI arthritis patients, median (interquartile range) time of onset was 3 (1.3–12) months after ICI initiation.[23] There can be a very long delay between ICI arthritis onset and referral to a rheumatologist, as shown by Cappelli and colleagues.[23] In that cohort, patients with knee arthritis generally were referred within 1 month to 2 months whereas there was a median delay of a

Table 3
Approach to the management of rheumatological immune-related adverse events

			Treatment		
	Clinical Examination	**Testing**	**Grade 1**	**Grade 2**	**Grade 3–4**
Arthritis	Look for swelling of small joints (MCP, PIP, wrists), tendons (eg, at the wrists, patella, quadriceps, triceps)	CBC ESR CRP RF CCP ANA	NSAIDS, Intraarticular injection Prednisone 5–10 mg if needed If unable to taper steroids, consider hydroxychloroquine, sulfasalazine	NSAIDS, Intraarticular injection Prednisone 10–30 mg If unable to taper steroids, consider hydroxychloroquine, sulfasalazine, methotrexate, TNFi, IL-6Ri	NSAIDS, Intraarticular injection Prednisone 30–60 mg If unable to taper steroids quickly, consider TNFi, IL- 6Ri. MTX
	Extra-articular features (eg, psoriasis)		Continue ICI	Hold ICI, rechallenge when prednisone 10 mg or less	Hold ICI
PMR	Pain on ROM shoulders and hips Evaluate for signs of GCA (headache, temporal artery tenderness)	CBC ESR CRP RF CCP	NSAIDS, Subacromial bursa injection Prednisone 5–20 mg daily If unable to taper steroids, consider hydroxychloroquine, MTX	NSAIDS Prednisone 20–40 mg If unable to taper steroids, consider MTX, IL-6Ri	NSAIDS, Prednisone 40–60 mg If unable to taper steroids, consider IL-6Ri
			Continue ICI	Hold ICI	Hold ICI
Activated OA	Pain in joint previously affected by OA, usually hip or knee	X-ray Joint aspiration to rule out inflammatory arthritis, crystal disease	NSAIDS, Intraarticular steroid injection (US guided in the case of the hip)	NSAIDS, Intraarticular injection (US guided in the case of the hip) Consider prednisone 5–10 mg daily Consider orthopedic referral	NSAIDS, Intraarticular injection (US guided in the case of the hip) Consider prednisone 10–20 mg daily Consider orthopedic referral

Sicca	Dry oral mucosa, parotid gland swelling, gritty sensation in eyes	CBC, ESR, CRP, ANA, RF, SSA (Ro), SSB (La) antibodies	Biotin rinse Cevimeline or pilocarpine	Prednisone 10–30 mg daily	Prednisone 1 mg/kg
	(The presence of blistering or ulceration suggests pemphigoid not sicca.)		Continue ICI	Hold ICI; may be able to resume once steroid dose is tapered low enough	Hold ICI
Myositis	Muscle, joint and neurologic examination, assess for dysphagia and dysphonia, extraocular muscle function Skin examination (consider dermatomyositis)	CK, troponin, transaminases, CBC, ESR, CRP, antistriated muscle, acetylcholine receptor, and myositis antibody panel Echocardiogram and EKG to screen for concomitant myocarditis. NIFs if evidence of respiratory compromise, swallowing evaluation if dysphagia Consider EMG, MRI, and/or muscle biopsy	If myalgia only, NSAIDs, can be used If CK elevation but no muscle weakness, prednisone 10–20 mg daily If muscle weakness, then treat as grade 2	Prednisone 0.5–l mg/kg daily Rheumatology and/or neurology consultation Cardiology consult if troponin elevation	Methylprednisolone 1 g IV and then 1 mg/kg, consider IVIG or PLEX Consider methotrexate, azathioprine, mycophenolate mofetil If refractory, consider rituximab. Rheumatology and/or neurology consultation Cardiology consult if troponin elevated
			Continue ICI	Hold ICI, may consider re-challenge if no cardiac or bulbar involvement	Discontinue ICI

(*continued on next page*)

Table 3
(*continued*)

			Treatment		
	Clinical Examination	**Testing**	**Grade 1**	**Grade 2**	**Grade 3–4**
Eosinophilic fasciitis	Skin thickening and tethering Pain in limbs Loss of range of motion of the joints due to tightening of the fascia Sparing of the hands and face	CBC with eosinophil count, ESR, CRP, CPK Consider MRI Consider deep skin biopsy	Consider 0.5 mg– 1 mg/kg prednisone daily with taper Consider phototherapy Continue ICI	Consider 1 mg/kg prednisone Consider addition of DMARD, such as methotrexate, mycophenolate mofetil, dapsone Hold ICI	Pulse-dose steroids DMARD therapy, consider cyclophosphamide Rheumatology and dermatology consultation Hold ICI
GCA	New headache, loss of vision, jaw claudication, temporal tenderness, scalp tenderness, neck pain, symptoms of PMR	CBC with diff, CMP, ESR, CRP c-ANCA Temporal artery biopsy Bone densitometry	Not applicable/NA	1mg/kg prednisone daily with taper Calcium–vitamin D Consider bisphosphonate if on steroid monotherapy Strongly consider IL-6Ri Hold ICI	ER/hospital admission Pulse-dose steroids Strongly consider IL-6Ri, Calcium/vitamin D Consider bisphosphonate if on steroid monotherapy Rheumatology, ophthalmology consult Hold ICI
Sarcoidosis	Fatigue, weight loss, malaise, cough, myalgias, weakness, arthralgias or arthritis, rash	CBC with diff CMP, including calcium ESR CRP CPK, ACE level Chest radiograph Consider skin or transbronchial biopsy	No treatment necessary unless symptomatic NSAIDs Topical steroids Hydroxychloroquine Consider prednisone 5–10 mg for joint pain or other mild symptoms Continue ICI	Consider prednisone 10–30 mg daily Topical steroids Hold ICI; may be resume ICI once steroid dose is low enough	Consider 0.5–1 mg/kg prednisone or higher Consultation with rheumatology, dermatology or pulmonology Hold ICI

Abbreviations: ACE, angiotensin-converting enzyme; ANA, anti-nuclear antigen; CK or CPK, creatine phosphokinase; CMP, complete metabolic panel; CRP, C-reactive protein; diff, differential; EKG, electrocardiogram; ER, emergency room; ESR, erythrocyte sedimentation ratio; IV, intravenous; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; N/A, not applicable; NIF, negative inspiratory force; OA, osteoarthritis; PIP, proximal interphalangeal; PLEX, plasmapharesis; ROM, range of motion; US, ultrasound.

year before referral of patients with arthritis of the small joints of the hands. Oncologists have become more aware of ICI arthritis in recent years, however.

Just as inflammatory arthritis can take different forms in the non-ICI setting (eg, rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis), ICI arthritis also has a variety of presentations (see **Fig. 1**). Approximately two-thirds of ICI arthritis patients have a rheumatoid arthritis–like presentation with symmetric involvement of the MCP and PIP joints and wrists as well as larger joints.[6,23,30,31] Some patients have joint pain (arthralgia) and morning stiffness but no objective joint swelling. Another phenotype is a large joint arthritis, affecting the knees in particular, sometimes with accompanying tenosynovitis (swelling in the tendon sheath) or enthesitis (pain where tendons insert on bone) and, rarely, with concomitant psoriasis. Tenosynovitis/enthesitis also can occur in the absent of arthritis. Large joint arthritis seems more common after combination ICI than ICI monotherapy.[23] Although the large joint phenotype is reminiscent of spondyloarthropathies, patients generally are HLA-B27 negative.[32]

Laboratory testing in patients with ICI arthritis sometimes, but not always, shows elevated inflammatory markers. Joint fluid is inflammatory but there are no unique synovial fluid findings in this condition. The frequency of rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (CCP) varies from cohort to cohort. In a series of ICI arthritis patients from Baltimore, only 3% were seropositive,[23] whereas seropositivity was approximately 30% in a Munich cohort.[32] In a systematic review of case series and case reports, 9% of patients with ICI arthritis were RF positive and/or CCP positive.[30] Whether these patients had preexisting autoantibodies or whether they seroconverted after ICI initiation is not known. ICIs have been shown to induce autoantibody seroconversion, including RF and CCP, but in 1 study of 121 patients treated with ipilimumab (anti–CTLA-4), none of the 3 patients who developed RF/CCP antibodies developed ICI arthritis, whereas the 3 patients developed arthralgia or arthritis remained seronegative.[33]

Thirty years ago, Gregersen and colleagues[34] demonstrated an association between rheumatoid arthritis and the shared epitope, a 5–amino acid motif found in certain HLA-DRB1 alleles. Later, the genetic association with rheumatoid arthritis was shown to be limited to CCP-positive patients, in particular smokers.[35] In a study of 26 patients of European descent with ICI arthritis from the Baltimore cohort, heterozygosity for the shared epitope was twice as common as in healthy controls (and comparable to patients with RA), even though only 4 of the patients were seropositive (2 CCP and 2 RF).[36] This suggests there are both shared and unshared mechanisms underlying ICI arthritis and RA, and this ultimately may add to understanding of rheumatoid arthritis pathogenesis. A gene signature that has been shown to be upregulated in cancer patients treated with nivolumab (anti–PD-1) also has been shown to be upregulated in patients with active RA,[37] again suggesting some shared pathophysiologic mechanisms.

Approach to the patient History and physical examination should be performed to determine the particular joints that are affected and disease severity. The CTCAE grading system defines grade 1 arthritis as mild pain with inflammation, erythema, or joint swelling; grade 2 as moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental activities of daily living (ADLs); and grade 3 as severe pain associated with signs of inflammation, erythema, or joint swelling, irreversible joint damage, limiting self-care ADLs (CTCAE).[9] As noted previously, measuring arthritis activity using the CDAI is helpful in measuring response to treatment.[19]

Laboratory testing can corroborate the clinical assessment of disease activity, including a complete blood cell count (CBC), C-reactive protein (CRP), and an erythrocyte sedimentation rate (ESR). Creatinine kinase (CK) testing is useful to rule out concomitant myositis. The authors generally test for CCP, RF, and antinuclear antibody (ANA). Testing for hepatitis B and hepatitis C and screening for tuberculosis exposure are useful at baseline, in case a patient ultimately requires DMARDs, such as methotrexate, or a TNFi. Radiographs or ultrasound of the hands should be performed in patients with small joint involvement to look for evidence of erosive disease. Many patients have prominent knee joint involvement and baseline radiographs of the knees also can be useful in that setting.

Treatment One of the distinguishing characteristics of ICI arthritis is its tendency to persist.[27] For this reason, DMARDs often are added early on in the course of treatment, even if symptoms are not severe, in order to spare patients long-term treatment with corticosteroids.

The overall approach to treatment is summarized. Grade 1 arthritis sometimes can be managed with NSAIDs and intraarticular steroid injections but may require the addition of low-dose oral corticosteroids (prednisone 5–10 mg daily or the equivalent). ICIs generally can be continued in this setting. If corticosteroids cannot be tapered after 1 month to 2 months, a mild DMARD, such as hydroxychloroquine or sulfasalazine, can be considered. These agents take 2 months to 3 months to have their effect but may be steroid sparing. In 1 series of 11 ICI arthritis patients treated with hydroxychloroquine and corticosteroids, 7 had control of their symptoms on treatment with this regimen.[38] Grade 2 arthritis may require higher doses of corticosteroids, up to 30 mg daily, and temporary holding if ICI. If corticosteroids cannot be tapered to 10 mg daily within 2 to 3 weeks, the authors generally add a steroid-sparing DMARD, which could include hydroxychloroquine, sulfasalazine, methotrexate, or a TNFi. Grade 3 arthritis requires treatment with high-dose corticosteroids. If symptoms are not controlled easily within 1 week to 2 weeks, the authors recommend treatment with a TNFi because of their rapid onset of action. Methotrexate can be added if there is only a partial response but takes 2 months to 3 months to have its effect. Patients who are refractory to TNFi can be switched to an interleukin (IL)-6R blocker, such as tocilizumab or sarilumab. In a published series of 3 ICI arthritis patients treated with tocilizumab, all had a clinical response to the drug, but 2 of 3 had cancer progression.[39] For this reason, the authors generally do not use IL-6R blockade as first-line therapy.

Polymyalgia Rheumatica

In the authors' systematic literature review of case series and case reports of ICI-associated musculoskeletal complaints, 78/372 (21%) had symptoms consistent with PMR.[30] As with PMR outside the ICI setting, ICI-associated PMR sometimes can be associated with some hand pain and swelling, suggesting some overlap with RA, and occasionally patients have a positive RF or CCP.[40] A diagnosis of ICI-associated PMR is a clinical one, based on the distribution of joint pain and stiffness (shoulders, neck, hips, thighs, and low back [see **Fig. 2**]). Acute-phase reactants may or may not be elevated.[40] As with patients with ICI-associated arthritis, the authors generally send a CBC, CK ESR, CRP, RF, and CCP. Given proximal limb involvement in ICI-associated PMR, it is important to consider myositis in the differential diagnosis. In contrast to patients with PMR, patients with myositis typically complain of weakness, which may be demonstrated on examination, and CK is elevated.

A majority of patients with ICI-associated PMR respond to corticosteroids alone but in 1 large case series, approximately half of the patients required more than 20 mg of prednisone daily,[40] more than typically is required for PMR. In the non-ICI setting, PMR can be associated with giant cell arteritis (GCA) in a small percentage of patients. GCA rarely has been described in patients treated with ICI,[41,42] even without elevated inflammatory markers, so it is important to ask any patient with symptoms of ICI-associated PMR whether they have cranial symptoms, such as temporal headache, scalp sensitivity, or jaw claudication. The presence of these symptoms mandate treatment with high-dose corticosteroids (prednisone, 60 mg daily) and prompt referral to a rheumatologist. Patients with ICI-associated PMR or GCA who require high-dose corticosteroids, or are unable to taper corticosteroids, can be treated with IL-6R blockade.[40] In milder cases, hydroxychloroquine or methotrexate can be used as a steroid-sparing agent.

Activated osteoarthritis

ICI-treated patients sometimes can present with severe pain in a single large joint, such as the hip or knee, and have evidence of osteoarthritis on radiographs of the affected joint. If synovial fluid analysis does not demonstrate inflammation, the authors refer to this painful condition as "activated osteoarthritis" (assuming metastatic disease and avascular necrosis have been ruled out). Most of these patients have had prior radiographs demonstrating osteoarthritis that predated treatment with ICI. With ICI treatment, however, they became more symptomatic or, less commonly, newly symptomatic. Painful flares of osteoarthritis in the non-ICI setting have been linked to inflammation at the microscopic level,[43] and it is likely that low-grade or subclinical inflammation is responsible for this ICI-associated phenomenon as well. Patients can be managed with NSAIDs and/or analgesics. Intraarticular injection of corticosteroids can be helpful. In cases of hip involvement, injections should be guided by ultrasound or fluoroscopy. Although the authors try to avoid systemic corticosteroids, at times a small dose of prednisone may be needed, especially if ICIs are continued. In cases of very advanced osteoarthritis, some patients may consider joint replacement, taking into consideration the prognosis of their malignancy.

Myositis

Myalgias (muscle pain) with or without CK elevation is reported in more than 20% of patients receiving nivolumab whereas true myositis, with muscle inflammation, weakness, and elevated CK occurs in less than 1% of patients who undergo therapy with a PD-1 inhibitor.[44] ICI-associated myositis often occurs early, within a month of ICI initiation.[45] Presentations can range from asymptomatic CK elevation to fulminant, diffuse weakness requiring ventilatory support. Although some patients present with proximal muscle weakness and elevated CK typical of de novo polymyositis, atypical muscle involvement also is described, including the of periorbital, bulbar, or paraspinal muscles, and CK sometimes can be severely elevated, up to 75 times the upper limit of normal, and associated with rhabdomyolysis.[46] Myositis-associated antibodies (such as antisynthetase antibodies) have been reported in some but not all series.[46,47] Patients with ICI myositis often have features of myasthenia gravis, such as diplopia and ptosis, although the results of electromyography (EMG), edrophonium (Tensilon) test, or cold pack testing not always are typical of those seen in de novo myasthenia.[45] Antistriated muscle antibodies commonly are seen in ICI myositis patients with features of myasthenia gravis, but antibodies to acetylcholine receptor are rarer. Patients with ICI myositis can have subtle (and not so subtle) concomitant myocarditis, and the converse also is true. According to a World Health Organization registry of myocarditis

patients, 25% also had myositis.[48] ICI myocarditis is critical to identify because of its high case fatality rate, often due to arrhythmia. ICI myocarditis generally is associated with an elevated troponin I level, with or without changes on electrocardiography (EKG) or echocardiography.[49,50] Changes in EKG and/or echocardiography not always are present and cardiac MRI may be unremarkable, even in cases where endomyocardial biopsy shows inflammation.[19,51]

Muscle pathology in patients with ICI myositis demonstrates infiltration by histiocytes and cytotoxic T cells.[45] One autopsy study of 2 patients with ICI myositis demonstrated shared $CD8^+$ T-cell clones in the tumor, heart, and skeletal muscle, suggesting the possibility of muscle injury due to cross-reactive T cells between the tumor and muscle.[52]

Treatment of ICI myositis depends on the severity of symptoms. Myalgia alone can be treated with NSAIDs or low-dose steroids, and ICI treatment does not need to be held unless there is severe pain and/or true muscle weakness. Patients with significant proximal weakness or any combination of the triad of myositis, myasthenia, and/or myocarditis require hospitalization and urgent treatment with high-dose corticosteroids. Some patients require intravenous immunoglobulin and/or plasmapheresis and immunosuppressive agents, such as mycophenolate mofetil.

Finally, although it can be difficult to distinguish ICI-induced myositis from a paraneoplastic inflammatory myositis clinically, the timing of myositis symptoms can help differentiation the 2—ICI myositis is likely to start within 1 month to 2 months of ICI treatment.[45–47] Dermatomyositis, which is more commonly paraneoplastic than polymyositis, is seen only rarely after ICI treatment.

Sicca disease

Sicca disease, or sicca syndrome, refers to dryness of the mouth and/or eyes due to exocrine gland dysfunction, symptoms that are typical of de novo Sjögren syndrome. ICI-associated sicca predominantly affects the mouth in contrast to non–ICI-related Sjögren, which results in dryness of both the eyes and mouth.[53] Sicca can follow treatment with both anti–PD-1/PD-L1 and anti–CTLA-4.[40,53] In clinical trials, the incidence of sicca in ICI-treated patients can be as high as 24%, although more often it affects 3% to 8% of treated patients.[40,54] Patients often report dry, cracked lips, difficulty chewing and swallowing food, altered taste, hoarseness, and difficulty swallowing food. When dryness affects the eyes, they often are described as gritty, with a sandlike sensation in the eye. Severe cases can lead to tongue fissuring and cavitation. It is important to rule out other causes of mouth irritation and pain, including pemphigoid (which also is seen in ICI-treated patients)[55] or concomitant chemotherapy causing stomatitis. Parotid swelling rarely is reported in ICI-treated patients, in contrast to de novo Sjögren syndrome. Occasionally, patients with ICI-associated sicca can have concomitant arthralgias but Sjögren antibodies (SSa/Ro and SSb/La) are present only rarely. Salivary gland histopathology demonstrates infiltration by T cells, and a notable absence of B cells, unlike de novo Sjögren, where infiltrating B cells predominate and germinal centers can be seen.[53]

Treatment of sicca depends on the severity of symptoms. Mild symptoms (grade 1, intermittently symptomatic without significant dietary alteration or visual disturbances) do not require the interruption of ICI therapy and can be treated with basic oral care, including good dental hygiene and the use of Biotene, an alcohol-free moisturizing mouthwash. Sugarless gum or sugar-free hard candy also can stimulate saliva production. Maintaining adequate hydration also is encouraged. Mild dry eye can be treated with over-the-counter refreshing eye drops. Moderate symptoms (grade 2, symptomatic with slightly altered oral intake and mild–moderate decrease in visual

acuity) usually also do not require the interruption of ICI therapy and build on top of basic oral care with the addition of sialagogues, such as pilocarpine or cevimeline. Low-dose to moderate-dose corticosteroids may be required if symptoms persist. Severe symptoms (grade 3, interfering with ADLs, such as eating, speaking, and seeing) require cessation of ICI treatment and high-dose corticosteroids. Initial prednisone doses, of 20 mg per day to 40 mg per day for 2 weeks to 3 weeks, with a taper to follow, have shown favorable responses if treatment is started early.[53] Consultation with a dentist and/or ophthalmologist is recommended for patients with moderate or severe symptoms and when advanced therapies are needed, such as punctal plugs for severe dry eye. Although patients often improve symptomatically, salivary flow may not normalize.

Miscellaneous Rheumatic Disease

Sarcoid

Sarcoidosis or sarcoid-like reactions are not uncommon in ICI-treated individuals. Patients can present with rash or nodules, cough, arthralgias/arthritis, or inflammatory eye disease. Less commonly, granulomatous inflammation may be demonstrated in the spleen, bone marrow, or central nervous system.[56] Some patients are asymptomatic, however, and are diagnosed pathologically when noncaseating granulomas are found on biopsies done to evaluate changes on routine surveillance imaging, such as lymphadenopathy or pulmonary nodules. ICI sarcoid generally is steroid-responsive with steroid doses determined by the severity of symptoms, if there are any.[57] Treatment is not necessary in the absence of symptoms or other functionally significant changes. ICI sarcoid is not more common with anti–PD-1/PDL-1 or anti–CTLA-4 and there is no gender predisposition. Melanoma patients may be more likely to develop ICI sarcoid because they have an already higher incidence of sarcoidosis compared with the general population,[56] but melanoma patients also are the population most commonly treated with ICIs.

Vasculitis

Several case reports of vasculitis after ICI therapy have been described, including cutaneous leukocytoclastic vasculitis, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss), granulomatosis with polyangiitis (formerly known as Wegener), GCA, and cryoglobulinemic vasculitis.[54] Typical symptoms of vasculitis, such as arthralgias or arthritis, palpable purpura, myalgias, fever, weight loss, and fatigue, have been described, although presentations vary. Although these manifestations have been described, vasculitis as an entity arising from ICI remains very rare. Serologies rarely are positive, so biopsy often is needed to establish a diagnosis.

Fibrosing skin disorders

Skin thickening has been reported as a rare rheumatic irAE, most commonly eosinophilic fasciitis rather than scleroderma. Eosinophilic fasciitis can result in severe joint contractures, pain, and muscle inflammation, and early recognition is important to minimize long-term morbidity.[58]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) rarely is reported after ICI treatment, perhaps because ICI treatment is associated with high levels of interferon (IFN)-gamma rather than IFN-alpha, the putative driver of SLE. Subacute cutaneous lupus erythematosus has been described in a few ICI-treated patients presenting as the typical annular or psoriasiform eruption with an interface dermatitis on biopsy. Hydroxychloroquine and/or low-dose steroids can be used to treat these rare cases.

SUMMARY

In summary, there are a variety of rheumatic complications that can arise from treatment with ICI, with inflammatory arthritis and PMR the most common. ICI arthritis can affect quality of life significantly, and, although it usually can be treated rapidly and effectively, symptoms often persist and can require long-term treatment with corticosteroids and/or the addition of steroid-sparing agents. ICI myositis can have varying presentations from asymptomatic CK elevation to florid respiratory failure with diaphragmatic weakness as well as overlap symptoms with myocarditis and myasthenia gravis. Sicca symptoms after ICI vary in severity but at times require treatment with corticosteroids to prevent exocrine gland failure. SLE is extremely rare rheumatic after ICI, which may provide clues to the mechanism underlying irAEs.

CLINICS CARE POINTS

- When evaluating a patient with musculoskeletal pain, it is important to identify the affected organ—joint, muscle, nerve, or tendon.
- Joint pain after ICI can be inflammatory or mechanical and can be differentiated by the presence of swelling, morning stiffness greater than 30 minutes, and the pattern of joint distribution.
- PMR can be seen as a consequence of ICI therapy but may require higher doses of corticosteroids than are needed outside the ICI setting.
- Myositis often presents with myalgias, proximal muscle weakness, and elevated CK, but myasthenia-like bulbar and ocular involvement are common, as is concomitant myocarditis, and these overlap syndromes have a high fatality rate.
- Treatment of rheumatic irAEs always should be discussed with a patient's oncologist, and early rheumatology consultation usually is advisable.

DISCLOSURE

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REFERENCES

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373(1):23–34.
2. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359(6382):1350–5.
3. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27(4):450–61.
4. Marcus L, Lemery SJ, Keegan P, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res 2019;25(13):3753–8.
5. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol 2018;36(8):773–9.
6. Chan KK, Bass AR. Autoimmune complications of immunotherapy: pathophysiology and management. BMJ 2020;369:m736.

7. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378(2):158–68.
8. Arnaud-Coffin P, Maillet D, Gan HK, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer 2019;145(3):639–48.
9. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed June 18, 2020.
10. Sznol M, Ferrucci PF, Hogg D, et al. Pooled Analysis Safety Profile of Nivolumab and Ipilimumab Combination Therapy in Patients With Advanced Melanoma. J Clin Oncol 2017;35(34):3815–22.
11. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 2017;35(7):785–92.
12. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4(12):1721–8.
13. Zhou X, Yao Z, Yang H, et al. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med 2020;18(1):87.
14. Freeman-Keller M, Kim Y, Cronin H, et al. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes. Clin Cancer Res 2016;22(4):886–94.
15. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol 2015;33(7):773–81.
16. Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the Association Between Adverse Events and Outcome in Patients Receiving a Programmed Death Protein 1 or Programmed Death Ligand 1 Antibody. J Clin Oncol 2019;37(30):2730–7.
17. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. N Engl J Med 2019;380(24):2377–9.
18. Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review. Ann Intern Med 2018;168(2):121–30.
19. Leung AM, Farewell D, Lau CS, et al. Defining criteria for rheumatoid arthritis patient-derived disease activity score that correspond to Disease Activity Score 28 and Clinical Disease Activity Index based disease states and response criteria. Rheumatology (Oxford) 2016;55(11):1954–8.
20. Abu-Sbeih H, Ali FS, Wang X, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor–induced colitis. J Immunother Cancer 2019;7(1):93.
21. Johnson DH, Zobniw CM, Trinh VA, et al. Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis. J Immunother Cancer 2018;6(1):103.
22. Wang Y, Abu-Sbeih H, Mao E, et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. J Immunother Cancer 2018;6(1):37.
23. Cappelli LC, Brahmer JR, Forde PM, et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. Semin Arthritis Rheum 2018;48(3):553–7.

24. Smith MH, Bass AR. Arthritis after cancer immunotherapy: symptom duration and treatment response. Arthritis Care Res 2019;71(3):362–6.
25. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer 2018;124(18):3706–14.
26. Verheijden RJ, May AM, Blank CU, et al. Association of Anti-TNF with Decreased Survival in Steroid Refractory Ipilimumab and Anti-PD1-Treated Patients in the Dutch Melanoma Treatment Registry. Clin Cancer Res 2020;26(9):2268–74.
27. Braaten TJ, Brahmer JR, Forde PM, et al. Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. Ann Rheum Dis 2020;79(3):332–8.
28. Perez-Ruiz E, Minute L, Otano I, et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. Nature 2019; 569(7756):428–32.
29. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis 2018;77(3):393–8.
30. Ghosh N, Tiongson MD, Stewart C, et al. Checkpoint Inhibitor-Associated Arthritis: A Systematic Review of Case Reports and Case Series. J Clin Rheumatol 2020. https://doi.org/10.1097/RHU.0000000000001370. Epub ahead of print. PMID: 32345841.
31. Richter MD, Crowson C, Kottschade LA, et al. Rheumatic Syndromes Associated With Immune Checkpoint Inhibitors: A Single-Center Cohort of Sixty-One Patients. Arthritis Rheum 2019;71(3):468–75.
32. Leipe J, Christ LA, Arnoldi AP, et al. Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. RMD Open 2018;4(2):e000714.
33. de Moel EC, Rozeman EA, Kapiteijn EHW, et al. Autoantibody development under treatment with immune checkpoint inhibitors. Cancer Immunol Res 2019; 7(1):6–11.
34. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30(11):1205–13.
35. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54(1):38–46.
36. Cappelli LC, Dorak MT, Bettinotti MP, et al. Association of HLA-DRB1 shared epitope alleles and immune checkpoint inhibitor-induced inflammatory arthritis. Rheumatology (Oxford) 2019;58(3):476–80.
37. Guo Y, Walsh AM, Canavan M, et al. Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. PLoS One 2018;13(2):e0192704.
38. Roberts J, Smylie M, Walker J, et al. Hydroxychloroquine is a safe and effective steroid-sparing agent for immune checkpoint inhibitor–induced inflammatory arthritis. Clin Rheumatol 2019;38(5):1513–9.
39. Kim ST, Tayar J, Suarez-Almazor M, et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. Ann Rheum Dis 2017;76(12):2061–4.
40. Calabrese C, Cappelli LC, Kostine M, et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. RMD Open 2019;5(1):e000906.

41. Betrains A, Blockmans DE. Immune Checkpoint Inhibitor-Associated Polymyalgia Rheumatica/Giant Cell Arteritis Occurring in a Patient After Treatment With Nivolumab. J Clin Rheumatol 2019. https://doi.org/10.1097/RHU.0000000000001012. Epub ahead of print. PMID: 30801332.
42. Micaily I, Chernoff M. An unknown reaction to pembrolizumab: giant cell arteritis. Ann Oncol 2017;28(10):2621–2.
43. Scanzello CR. Role of low-grade inflammation in osteoarthritis. Curr Opin Rheumatol 2017;29(1):79–85.
44. <pi_opdivo.pdf>. In: Squibb B-M, editor. packageinserts. Available at: packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed October 23, 2020.
45. Seki M, Uruha A, Ohnuki Y, et al. Inflammatory myopathy associated with PD-1 inhibitors. J Autoimmun 2019;100:105–13.
46. Shah M, Tayar JH, Abdel-Wahab N, et al. Myositis as an adverse event of immune checkpoint blockade for cancer therapy. Semin Arthritis Rheum 2019;48(4):736–40.
47. Moreira A, Loquai C, Pföhler C, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Cancer 2019;106:12–23.
48. Moslehi JJ, Salem JE, Sosman JA, et al. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet 2018;391(10124):933.
49. Ganatra S, Neilan TG. Immune Checkpoint Inhibitor-Associated Myocarditis. Oncologist 2018;23(8):879–86.
50. Mahmoud F, Wilkinson JT, Gizinski A, et al. Could knee inflammatory synovitis be induced by pembrolizumab? J Oncol Pharm Pract 2018;24(5):389–92.
51. Escudier M, Cautela J, Malissen N, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. Circulation 2017;136(21):2085–7.
52. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med 2016;375(18):1749–55.
53. Warner BM, Baer AN, Lipson EJ, et al. Sicca Syndrome Associated with Immune Checkpoint Inhibitor Therapy. Oncologist 2019;24(9):1259–69.
54. Cappelli LC, Gutierrez AK, Bingham CO III, et al. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res 2017;69(11):1751–63.
55. Naidoo J, Schindler K, Querfeld C, et al. Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1. Cancer Immunol Res 2016;4(5):383–9.
56. Rambhia PH, Reichert B, Scott JF, et al. Immune checkpoint inhibitor-induced sarcoidosis-like granulomas. Int J Clin Oncol 2019;24(10):1171–81.
57. Gkiozos I, Kopitopoulou A, Kalkanis A, et al. Sarcoidosis-Like Reactions Induced by Checkpoint Inhibitors. J Thorac Oncol 2018;13(8):1076–82.
58. Chan KK, Magro C, Shoushtari A, et al. Eosinophilic Fasciitis Following Checkpoint Inhibitor Therapy: Four Cases and a Review of Literature. Oncologist 2020;25(2):140–9.