MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER (MASCC) 2020 CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF IMMUNE-MEDIATED CARDIOVASCULAR, RHEUMATIC AND RENAL TOXICITIES FROM CHECKPOINT INHIBITORS

Maria E. Suarez-Almazor[1], Xerxes Pundole[2], Noha Abdel-Wahab[3], Douglas B. Johnson[4], Dipti Gupta[5], Ilya Glezerman[6], Tim Cooksley[7], Ronald Anderson[8], Ada Blidner[9], Jennifer Choi[10], Michael Dougan[11], Pamela Ginex[12], Monica Girotra[13], Vickie R. Shannon[14], Bernardo L. Rapoport[8,15]

[1]Sections of Health Services Research and Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center, Houston, United States of America. msalmazor@mdanderson.org

[2]Section of Health Services Research, University of Texas MD Anderson Cancer Center, Houston, United States of America. XNPundole@mdanderson.org

[3]Section of Health Services Research, University of Texas MD Anderson Cancer Center, Houston, United States of America. NAHassan@mdanderson.org

[4]Department of Medicine, Vanderbilt University Medical Center and Vanderbilt Ingram Cancer Center, Nashville, Tennessee, United States of America. douglas.b.johnson@vumc.org

[5]Cardiology Division, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, United States of America. guptad@mskcc.org

[6]Renal Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, Ney York, United States of America. Glezermi@mskcc.org

[7]Manchester University Foundation Trust, Manchester, United Kingdom. The Christie, University of Manchester, Manchester, United Kingdom, cooks199@hotmail.com

[8]University or Pretoria, Faculty of Health Sciences, Department of Immunology, corner Doctor Savage Road and Bophelo Road, Pretoria 0002, South Africa. ronald.anderson@up.ac.za

[9]Laboratory of Immunopathology, Institute of Biology and Experimental Medicine-CONICET, Buenos Aires, Argentina.adablidner@gmail.com

[10]Division of Oncodermatology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America. jennifer.choi@northwestern.edu

[11]Massachusetts General Hospital, Boston, Massachusetts, United States of America. Harvard Medical School, Boston, Massachusetts, United States of America. mldougan@partners.org

[12]Oncology Nursing Society, Pittsburgh, Pennsylvania, United States of America. pginex@ons.org

[13]Endocrine Division, Department of Medicine, Weill Cornell Medical College (MG, AF), and Department of Medicine (DJB), Memorial Sloan-Kettering Cancer Center (MC), New York, Ney York, United States of America. girotram@mskcc.org

[14]Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, United States of America. vshannon@mdanderson.org

[15]The Medical Oncology Centre of Rosebank, 129 Oxford Road, Saxonwold 2196, Johannesburg, South Africa. bernardo.rapoport@up.ac.za

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Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; MES-A, XP, NA-W, DBJ, IG, TC shared sections on rheumatic immune-related adverse events equally, while BLR and DBJ provided clinical input and BLR, DBJ and RA editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

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Correspondence: Prof BL Rapoport

Department of Immunology

Faculty of Health Sciences

University of Pretoria

PO Box 667

Pretoria 0001

South Africa

Telephone: +27-11-880-4169

Email: bernardo.rapoport@up.ac.za

Abstract

Immune checkpoint inhibitors (ICIs) have emerged as the newest pillar of cancer treatment. Immune-mediated toxicities, stemming from increased activity within the T cell lineage, range from asymptomatic or mild complications to those that are fulminant and potentially fatal. Although they are of variable occurrence, cardiovascular, rheumatic, and renal immune-mediated toxicities are among the most serious of these adverse events. We present MASCC recommendations with respect to the workup and management of cardiovascular, rheumatic, and renal immune-mediated toxicities with a focus on presentations that require treatment with immunomodulating agents.

Keywords: arthralgia, arthritis, cardiomyopathy, corticosteroids, myocarditis, myositis, immunomodulation agents, other immunosuppressive agents, polymyalgia.

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as the newest pillar of cancer treatment [1]. Now approved in 16 different cancer types, these therapeutics may produce durable responses lasting for years in a subset of patients. Approved agents include those targeting programmed death-1 and its ligand (PD-1 and PD-L1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4). Combinations of anti-PD-1/PD-L1 with anti-CTLA-4 further augment immune responses and enhance clinical activity, but also increase the risk of toxicities.

Toxicities from ICIs are known as immune-related adverse events (IrAEs). These events result from a loss of self-tolerance when these key nodes of immune tolerance are pharmacologically inhibited [2,3]. IrAEs may affect essentially any organ system, and range from mildly symptomatic to fulminant and fatal [4,5].

In this section of the review of immune-related toxicities and recommendations for their management, we consider cardiovascular, rheumatologic and renal toxicities, focusing on the approach to the more severe presentations, which require corticosteroids and specialist management.

Cardiovascular Toxicities

As in other organ systems, IrAEs affecting the cardiovascular system tend to be inflammatory in nature. Myocarditis, the primary focus of this review, has been identified as a challenging syndrome, characterized by frequent and fulminant arrhythmias, variable declines in cardiac ejection fraction, and a high death rate [5-8]. Pericarditis and vasculitis have also been described as uncommon complications of therapy [9.] Despite these findings, the optimal diagnostic, screening, and therapeutic approaches remain relatively unclear. Herein, we review the literature to identify studies reporting these findings and posit recommendations for treating clinicians to effectively manage cardiovascular complications of ICI-based therapy.

Pathophysiology and epidemiology

Myocarditis appears to be the most common and serious cardiovascular toxicity from ICIs. Cases appear to be largely idiosyncratic, although myocarditis occurs more frequently with the combination of PD-1 and CTLA-4 blockade, as compared to ICI monotherapy [6,7]. Multiple pre-clinical studies have demonstrated a biologic plausibility for the role of immune checkpoints in the heart. For example, one of the first descriptions of the role of PD-1/PD-L1 signaling involved a knockout experiment of the gene for murine PD-1 (*Pdcd1*). Removing this gene resulted in an autoimmune dilated cardiomyopathy resulting from antibodies specific for troponin I [10,11]. Other pre-clinical experiments have implicated PD-1/PD-L1 signaling as being critical for prevention and mitigation of autoimmune myocarditis [12,13] and atherosclerosis [14,15].

Interestingly, myocarditis arising from ICI-targeted therapy has distinct features from the initial murine model (which was characterized by antibody deposits and B cells). At a molecular level, the inflamed myocardium is infiltrated by T cells (particularly CD8+ T cells) and macrophages without B cells or antibody deposits, although cases have been described where CD4+ T cells predominate [6,16]. Analyses of infiltrating T cells have shown substantial clonal overlap between the heart and inflamed tumor in some cases, potentially suggesting that a shared antigen between tumor and heart muscle may be targeted by culprit T cells [6].

However, the particular antigen(s) targeted by this aberrant immune attack is not clear at this time.

Several putative risk factors have been identified for ICI-myocarditis. The most well-defined is removal of multiple immune regulators by combining PD-1 and CTLA-4 blockade. Two separate series have shown an approximately 4-5-fold increase between anti-PD-1 monotherapy and combination PD-1/CTLA-4 blockade (0.06% vs. 0.27% in a large pharmacovigilance series which predated widespread awareness [6]; and 0.5% vs. 2.4% incidence in a single-center series with stringent monitoring) [7]. One series also suggested that the presence of diabetes might predispose patients, although this will need further validation [7]. It remains unclear whether prior cardiovascular disease or risk factors [5], or autoimmune disease [17,18], predispose patients to myocarditis. Having received an influenza vaccine appears not to be associated [19]. Similarly, it is not clear whether pre-existing viral infections (as in non-ICI myocarditis) are a risk factor for ICI-related myocarditis.

Clinical Presentation

Myocarditis occurs at a median of 25-34 days after initial ICI treatment, depending on the series [5,7,8]. This time of onset is generally earlier than most other toxicities [20]. Presenting symptoms include dyspnea (most common), fatigue, chest discomfort, or signs and symptoms of congestive heart failure. Troponin elevations are identified in the large majority of patients (>90%). Echocardiogram may show variable findings, often with preserved ejection fraction, and electrocardiogram (ECG) may show a variety of conduction system abnormalities. One unique feature of this clinical entity is the frequent concurrent skeletal muscle (myositis) and neuromuscular junction (myasthenia gravis) involvement. Due to diagnostic challenges (e.g., elevated creatinine kinase [CK] levels occur with both skeletal and cardiac muscle inflammation), available studies likely underestimate the concurrent nature of these events, which occur in at least 25% of cases [5,21]. The frequency of overlap, however, suggests that clinicians should assess for both syndromes if one is present (e.g. elevated CK and weakness, suggesting myositis should also trigger troponin and ECG evaluation to rule out myocarditis).

Many cases are fulminant in nature, with rapidly progressive refractory arrhythmias (conduction delays progressing to ventricular arrhythmias) presenting prior to decreased ejection fraction. Smoldering cases, however, with asymptomatic troponin elevation have also been described [22]. Fatality rates appear to be the highest of any published IrAEs, with up to 50% death rates reported [4]. Combination therapy may result in inferior clinical outcomes including initial oxygen requirement, myocardial changes on cardiac magnetic resonance (CMR), and higher admission troponin [5,7].

Screening and Diagnosis

Vigilance and prompt evaluation of ICI-myocarditis has been emphasized due to its aggressive and potentially fatal nature, given the association of better outcomes with early initiation of high-dose corticosteroids and immune-modulating agents [7,8]. Troponin and ECG are recommended as part of the initial diagnostic work-up for any suspected myocarditis and have also been proposed for screening asymptomatic patients on ICIs to establish an early diagnosis – an approach that has been endorsed by expert consensus statements [6,7,23,24]. However, recent cardiac surveillance data suggests ICI-myocarditis remains an uncommon entity and indiscriminate screening is low yield with majority of detectable or elevated troponin levels attributable to non-myocarditis or non-cardiac etiologies [25,26]. The utility of serial cardiac screening in cancer patients on ICI remains debatable, but baseline ECG and troponin in patients starting combination ICI can be useful [24].

Myocarditis should be suspected in all patients presenting with new or worsening cardiovascular or systemic symptoms who have a) started ICI therapy in the past 8 weeks b) have 1 or more non-cardiac IrAEs (especially myasthenia gravis or, myositis, colitis, or hepatitis) and c) have troponin elevations with atypical trends, especially with preserved left ventricular ejection fraction (LVEF) [6,7].

Myocarditis can be a diagnostic challenge with variable and complex clinical presentations. While ECG abnormalities and troponin elevations occur in majority of patients with ICI-myocarditis, these abnormalities must be interpreted in the clinical context and supported by complementary testing for definitive diagnosis [6,7].

Troponins are helpful not only for diagnosis, but also provide prognostic information with higher levels associated with worse outcomes [7]. New or worsening conduction system disease especially heart block, STT changes and arrhythmias on ECG or cardiac monitoring warrant urgent clinical attention [6-8].

Acute coronary syndrome, congestive heart failure, viral myocarditis, cardiac metastases and systemic illnesses such as pulmonary embolism, metabolic derangements, sepsis, stroke and pneumonia form the differential diagnosis. Transthoracic echocardiography, cardiac magnetic resonance imaging (CMR) and endomyocardial biopsy (EMB) are frequently used to aid in the diagnosis. Transthoracic echocardiography is safe, widely accessible and provides information on left ventricular systolic function and regional wall motion in addition to valvular and pericardial disease [7,8]. Patients with ICI-myocarditis may have a preserved left ventricular ejection fraction, which can be falsely reassuring as these patients remain at risk for a fulminant course [6,7]. Other cardiac biomarkers, including natriuretic peptides can be useful, especially in patients with suspected heart failure [7,8]. Continuous cardiac monitoring for detection of malignant arrhythmias and heart block is recommended for hospitalized patients since electrical instability is a potentially life-threatening complication [6,7].

In hemodynamically stable patients, CMR is considered the non-invasive modality of choice to diagnose myocarditis, but limitations include accessibility and tolerability. Multiple pre- and post-contrast imaging sequences are utilized in conjunction to characterize inflammatory hyperemia, myocardial edema and fibrosis/scar [27]. A validated set of cardiac MRI parameters (Lake Louise Criteria) using T1-weighted early gadolinium enhancement, late gadolinium enhancement (LGE), and T2-weighted edema imaging have been derived from cases of suspected myocarditis in the general population [27]. The presence of 2 of the 3 of these criteria results in a sensitivity of 67% and a specificity of 91% for diagnosis of biopsy-proven myocarditis [27]. In addition to diagnostic capabilities, CMR also has prognostic implications with LGE positivity associated with worse outcomes in patients with myocarditis [28,29].

Endomyocardial biopsy is considered the gold standard for diagnosis of myocarditis; however, challenges include the need for technical expertise, risk of procedural complications and sampling errors [30]. Since there is a lack of literature examining the diagnostic utility of EMB in ICI-myocarditis, current clinical algorithms have been informed by extrapolation of non-ICI myocarditis data [30,31]. We recommend EMB be considered in a) clinically unstable patients who need acute mechanical circulatory support and/or coronary angiography and b) symptomatic patients with suspected myocarditis who are ineligible or unable to establish the diagnosis on CMR as confirmation of the diagnosis has important implications on management. The role of EMB in asymptomatic patients with CMR-negative, subclinical myocarditis with minor troponin elevations is not well established and warrants shared decision making with careful discussion of the risks and benefits with the patient.

Treatment

Although the optimal treatment strategy remains poorly defined, some general principles have emerged for treatment of ICI-myocarditis. These recommendations for management are summarized in Table 1. First, the usual system for grading therapeutic toxicities (Common Terminology Criteria for Adverse Events) is less helpful in guiding patients toward treatment algorithms than for other IrAEs. For myocarditis, this system stratifies patients as asymptomatic, mild or moderate symptoms, or life-threatening consequences. Instead, we would propose grading based on 1) myocarditis with asymptomatic troponin elevations (“asymptomatic”) vs. 2) myocarditis with symptoms or signs concerning for clinical deterioration (e.g. arrhythmias or decreased ejection fraction; “symptomatic”). As noted in the “Diagnosis” section above, empiric treatment, while confirming this or alternative diagnoses, may be necessary.

A second principle of ICI-myocarditis treatment is extrapolating effective therapies for other IrAEs. High-dose steroids, the cornerstone of IrAE management, does appear to have some efficacy. Although the usual dosing range is prednisone 1-2mg/kg daily for most IrAEs, one retrospective series showed that higher doses

(methylprednisolone 1g per day) was associated with improved cardiovascular outcomes [7]. We would recommend this pulse dose for symptomatic myocarditis. Asymptomatic disease can be managed with either standard dose or pulse dose corticosteroids in the absence of further data.

Table 1: Management of Cardiovascular IrAEs

CTCAE Grade	Grade 2	Grade 3/4
Cardiovascular		
Myocarditis Investigations	Electrocardiogram (ECG) Troponin, B Natriuretic Peptide Echocardiogram Consider Cardiac MRI	Cardiac MRI Endomyocardial Biopsy (EMB) Serial Troponins
Management	Oral Prednisolone (1mg/kg) Close monitoring	IV Corticosteroids (2mg/kg) Critical Care Monitoring Early immunosuppression (IVIg/ Tacrolimus/MMF) Consider Infliximab if preserved LV function Consider Abatacept in life-threatening/ refractory presentations

Of note, the impact of steroid treatment on ICI efficacy is not fully defined, including for patients with cardiovascular, renal, and rheumatic toxicities. Several studies have shown that patients who experience toxicities have equivalent or superior outcomes from those who have no toxicities. Similarly, patients who stop therapy early due to toxicities (and often require steroids) have equivalent outcomes compared with unselected patients. However, several complicating factors make it challenging to dissect the effects of steroids and toxicities. For example, do toxicities predispose to favorable outcomes which are partially ablated by steroids (as suggested by at least one study)? Are patients who have toxicities a biased cohort that remain on treatment longer because they are benefiting? These questions remained unanswered at this point.

Third, additional immunosuppression is often needed for ICI myocarditis and other severe adverse events. There are several candidates for second-line immunosuppressants. Infliximab is commonly used for colitis and pneumonitis, although it is contraindicated in patients with decreased ejection fraction, and has unclear utility in this setting. Mycophenolate mofetil is used for hepatitis and many other toxicities, although the oral administration and slower time to onset may make

this a less desirable agent [32]. Intravenous immunoglobulin (IVIg), anti-thymocyte globulin, tacrolimus, and abatacept have also been used with variable success, in small numbers [22,33-36]. We would advocate for use of a second immunosuppressant in symptomatic myocarditis, particularly in life-threatening cases. Although evidence for a preferred agent is scant, we would recommend IVIg, mycophenolate mofetil, or abatacept.

Fourth, cessation of ICI-based therapy is a key component of myocarditis management. Extensive studies have shown that patients who stop therapy early for toxicities (particularly patients treated with combination checkpoint blockade) may have equivalent outcomes to patients who complete therapy [37-39]. Admittedly though, myocarditis occurs often after one or 2 doses, and the impact of early discontinuation and multi-agent immunosuppression (as frequently occurs in ICI-myocarditis) on anti-tumor outcomes has not been well studied. Thus, for symptomatic cases, we would recommend permanent discontinuation of administration of ICIs. If no other options for cancer treatment exist, particularly for patients with an initial response followed by progression after cessation, a careful discussion of risks and benefits should be pursued prior to re-initiating therapy. Based on our experience, the risk of a recurrent event is very high in this setting (although again in relatively limited patient numbers). In patients with asymptomatic myocarditis, the situation is less clear, and resumption could potentially be considered if there is compelling clinical rationale, lack of viable alternatives, and complete resolution of myocarditis. However, even this scenario is likely high risk. Finally, the safety of resuming single agent anti-PD-1-targeted therapy following myocarditis arising from combination therapy is also unclear. One study suggests that toxicities occurring with combination immunotherapy often do not recur when monotherapy is restarted [40], although myocarditis has not been studied in this context and it is likely that the risk of recurrence is dependent on the specific toxicity examined. As with the above scenarios, we would strongly advise caution and would avoid re-challenge in the absence of a compelling clinical rationale, lack of other active options, and careful discussion of risks and benefits.

Finally, supportive management is essential for patients with ICI myocarditis. Continuous telemetry monitoring and electrophysiologic support (including

placement of defibrillator and/or pacemaker) is essential given the high rate of severe arrhythmias. Diuretics and afterload reduction may be needed in cases where congestive heart failure predominates. Concurrent myositis and/or myasthenia gravis may involve respiratory muscles and necessitate mechanical ventilation. Multidisciplinary management with cardiology and potentially other specialists (critical care, neurology) is essential given the severity of these presentations.

Although no rigorous, high-level evidence exists to guide management of myocarditis, or most other IrAEs, retrospective data and expert opinion can offer some guidance for clinicians treating patients suffering from these conditions. Myocarditis is a particularly difficult entity given its challenging diagnosis, high death rate, and relatively uncommon nature. The cornerstone of screening and diagnosis is troponin testing followed by biopsy or MRI confirmation. Treatment recommendations depend on severity, but are centered around immunosuppression (high-dose steroids plus other agents), cessation of ICIs, and multidisciplinary intensive supportive management. Additional studies are needed to determine optimal prediction, screening, diagnostic, and treatment approaches.

Rheumatic Toxicities

The most commonly reported rheumatic IrAEs include arthralgia and arthritis, polymyalgia rheumatica-like manifestations, and myositis. A variety of other rheumatic and connective tissue diseases has also been occasionally reported with the use of ICIs, such as sicca (Sjogren-like) syndrome, sarcoidosis, vasculitis, or lupus erythematosus [41-43]. Furthermore, bone-related adverse events such as fractures and osteonecrosis have also been described [44]. However, for these rare events, attribution to ICI therapy may be difficult, given their low frequency and lack of adequate controls of untreated patients.

There is a lack of evidence on best practices to treat rheumatic IrAEs, as most of the data on management is from small, uncontrolled case series. There are no clinical trials of therapeutic alternatives for the management of these adverse events. Management guidance has been based primarily on expert panel recommendations. We reviewed the pertinent literature, and of 208 initially retrieved publications, we

evaluated various publications that provided guidance on the management of rheumatic IrAEs, sponsored by the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the Society for Immunotherapy of Cancer (SITC), the National Comprehensive Cancer Network (NCCN) and Cancer Care Ontario (CCO) [24, 45-49]. We also identified several systematic reviews and case series reporting rheumatic adverse events following ICI therapy [41-43, 50-60]. Our recommendations are based on prior guidance and on case series reporting on empirical treatment of patients with rheumatic IrAEs.

We describe below the most common rheumatic manifestations after ICI therapy, summarizing the available recommendations for management.

Arthralgia and arthritis

Epidemiology

Arthralgia is the most common rheumatic IrAE reported in clinical trials, with a frequency as high as 40%. Inflammatory arthritis, with joint swelling, is less frequent, reported in about 3-5% of treated patients [41-43]. Arthralgia and arthritis are more common with PD-1 and PD-L1 blockers, when compared with anti-CTLA4 antibodies. Arthritis can occur at any time during ICI therapy, and has also been reported after discontinuation of ICI treatment.

Clinical Manifestations

Arthralgia is usually generalized and can involve large and small joints. Arthritis can present in different patterns [46, 52-54, 62-65]:

1) Oligoarticular arthritis (< 5 joints involved), generally affecting medium or large joints, such as knees, wrists or ankles;

2) Undefined polyarthritis affecting 5 or more joints with no specific pattern;

3) Spondyloarthritis, including psoriatic arthritis and reactive arthritis, which can have systemic features such as conjunctivitis and urethritis. These patients can also have sacroiliac, lumbar or cervical pain;

4) Rheumatoid arthritis, as defined by the American College of Rheumatology [66], affecting small joints in hands and/or feet symmetrically, and other peripheral joints;

5) Unusual arthritis presentations: tenosynovitis, enthesitis, and remitting sero-negative symmetrical synovitis (RS3PE) have been described in a few case reports.

Patients who develop rheumatoid arthritis are usually seropositive for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Patients in the other presentation groups are typically sero-negative.

Most often, patients with arthritis IrAE do not have associated radiographic abnormalities at diagnosis, although erosions have been reported occasionally.

While arthritis may resolve with ICI discontinuation and appropriate management, some patients develop chronic arthritis that requires therapy for months. One series suggested nearly half of patients develop chronic symptoms.

Diagnosis

The diagnosis of arthritis is based on clinical examination, by documenting pain and swelling in affected joints, after eliminating other potential diagnoses such as gout, pseudogout, septic arthritis, or metastatic involvement of the joints or bone in the affected areas [24, 45, 48, 49].

Laboratory tests that can aid in diagnosis and characterization of the arthritis include: RF, anti-CCP, antinuclear antibodies (ANA), and inflammatory markers such as erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). In patients presenting with lumbar or cervical pain, or reactive systemic manifestations, HLA B27 testing could potentially be useful to diagnose spondyloarthritis, although no cases of B27 positive patients have been reported.

Radiographic evaluation at baseline can be useful, as patients who respond poorly to treatment will require subsequent evaluation of radiographic joint damage. Musculoskeletal ultrasound and magnetic resonance imaging (MRI) are more sensitive than radiographs to evaluate synovitis and erosions and can also be useful to evaluate differential diagnoses.

Recommendation

These recommendations for management are summarized in Table 2. Early referral to a rheumatologist is recommended to establish a firm diagnosis and plan adequate treatment that aims to control symptoms and inflammation without dampening the immune response.

Grade 1 and 2. Arthritis can be treated with oral non-steroidal anti-inflammatory drugs (NSAIDS) and low-to-moderate dose corticosteroids (e.g prednisone ≤ 20mg). Intra-articular corticosteroid injections can be performed if there are only one or two joints involved. Therapy with ICIs can be continued if patients respond well to therapy.

Grade 3 and 4. These patients present with severe joint pain and swelling that interfere with their daily activities. In these patients, it is recommended to withhold ICI therapy. First line of therapy is oral corticosteroids at doses equivalent to 40 to 60 mg of prednisone, with tapering over the next 4 to 6 weeks. For some patients, especially those with other IrAEs or other comorbidities, intravenous corticosteroids may be appropriate. If there is no improvement and corticosteroids cannot be tapered successfully, a disease-modifying anti-rheumatic drug (DMARD) should be initiated. There is no clear evidence of what DMARD should be used first, as there are few published reports, which are not comparative and do not control for important confounders. Furthermore, there is no robust evidence on the potential effects of different DMARDs on anti-tumor immunity. The most frequently used DMARD has been low-dose methotrexate, which can be given orally in weekly doses ranging from 15 to 25 mg. Methotrexate can also be cautiously administered in weekly subcutaneous or intramuscular doses. Concomitant daily supplementation with folic acid is recommended as it can decrease methotrexate toxicity. Other synthetic DMARDs that have been used include hydroxychloroquine, sulfasalazine and leflunomide. Selected biologic DMARDs have also been used to treat refractory ICI-induced arthritis, including anti-tumor necrosis factor (TNF) agents (infliximab most often used), and tocilizumab, a humanized antibody against interleukin 6 receptor (IL-6R). These agents can be given intravenously or subcutaneously. Biologic DMARDs can result in substantially faster therapeutic responses than

synthetic DMARDs and may be the treatment of choice in severe cases with lack of response to corticosteroids.

Table 2: Rheumatic IrAEs. Management of Arthritis and Myositis.

Inflammatory Arthritis		
Investigations	CRP, ESR Autoantibodies Musculoskeletal Ultrasound	Musculoskeletal MRI
Management	Trial of NSAIDs Trial of low dose steroids (20mg) Consider intra-articular injections if only few joints affected	Oral Prednisolone 1mg/kg IV Corticosteroids (1-2mg/kg) Consider DMARD (Methotrexate) If refractory symptoms consider trial of Tocilizumab
Myositis		
Investigations	CK Autoantibodies (Myositis antibody) EMG Check Troponin	Musculoskeletal MRI Muscle biopsy
Management	Oral Prednisolone 1mg/kg	IV Corticosteroids (2mg/kg) IV fluids – Rhabdomyolysis regimen Plasmapheresis Consider IVIg or Infliximab Low threshold for Critical Care Monitoring

In patients whose arthritis resolves, re-initiation of ICI therapy may be considered. However, most patients who develop grade 3/4 arthritis may require concomitant corticosteroid or DMARD therapy during ICI administration to control arthritis flares, which could in theory hamper ICI-induced anti-tumor immunity.

Polymyalgia rheumatica (PMR)-like syndrome

Epidemiology

There have been several case reports and series of patients developing PMR-like symptoms during ICI therapy [53, 55-60]. The incidence of this IrAE is unknown as there are no robust cohort studies. This syndrome is possibly unrecognized and misclassified as severe arthralgia in clinical trials and in the initial reports of IrAEs in the literature, which have been increasing. Overall, there have been less than 50 cases reported. Most cases have been reported in patients receiving anti-PD-1

monotherapy, or combination therapy with anti-PD-1 and ipilimumab. PMR can occur at any time during ICI therapy, with a median of 3 months from therapy onset [67]..

Clinical Manifestations

Patients with ICI-induced PMR-like symptoms usually present with acute and severe pain and stiffness in the shoulders and/or pelvic girdle and hips, and fatigue [54, 58-61]. Although patients may report weakness, muscle strength is preserved, and what is described as weakness is primarily difficulty moving, because of stiffness and pain. Range of motion in the shoulders and hips can be limited. Primary PMR diagnostic criteria include absence of other joint involvement [67], but in ICI-induced PMR several patients have been reported to have concomitant arthritis, most commonly affecting the knees. Sub-deltoid bursitis and shoulder synovitis can also be present, contributing to the pain and stiffness. ICI-induced PMR presents more acutely and appears to be more severe than primary PMR. Giant cell arteritis is often associated with primary PMR, however, ICI-induced PMR typically presents without vasculitis.

Some patients will develop persistent symptoms despite discontinuation of treatment and may require prolonged therapy for several months.

Diagnosis

Differential diagnoses include myositis, which can also be induced by ICIs, and other causes of myalgia such as fibromyalgia, statin myopathy, and other articular and soft tissue rheumatic syndromes such as shoulder rotator cuff tendinitis, osteoarthritis or bursitis [24,46]. Although there are only a few cases reporting ICI-induced PMR with giant cell arteritis [69,70], all patients presenting with headache, visual disturbances or jaw claudication should be immediately evaluated by an ophthalmologist. If arteritis is suspected, a temporal biopsy should be performed, ideally before starting treatment, as vision loss can rapidly occur without treatment.

Laboratory testing should include creatine kinase (CK) levels. Patients with PMR have normal CK levels in contrast to those with myositis in whom CK is highly

elevated. Other baseline testing should include RF, anti-CCP and ANA, as these can be useful in the differential diagnosis, and are generally negative in PMR. Inflammatory markers including ESR and CRP should be measured as they aid in the differential diagnostic evaluation, and in disease activity monitoring. Markers are highly elevated in PMR, but may be normal or only slightly elevated in patients with mechanical soft tissue rheumatism such as rotator cuff tendinitis, or osteoarthritis.

Imaging with ultrasound or MRI can be useful in some patients to evaluate and monitor shoulder and hip bursitis or synovitis.

Recommendations [24,46].

Referral to a rheumatologist is recommended for prompt diagnosis and to differentiate between PMR and myositis or other causes of myalgia.

Grade 1 and 2. Most patients with some symptoms will require oral corticosteroids at a dose equivalent to 20 mg of prednisone, which can be tapered once symptoms improve after 3 or 4 weeks. Therapy with ICI may need to be withheld if symptoms do not resolve by the time of the next infusion; ICI can be restarted once corticosteroids can be tapered to a low dose ≤ 10 mg of prednisone. Steroid injections can be offered to patients with shoulder or trochanteric bursitis.

Grade 3 and 4. Patients with grade 3/4 PMR experience severe myalgia and stiffness that limits their mobility, ambulation, and daily activities. Checkpoint inhibitors should be withheld. These patients may require corticosteroids at higher dosages, equivalent to 40-60 mg of oral prednisone. For patients who do not respond to corticosteroids or who cannot be successfully tapered, DMARDs are an option, given the evidence for treatment in primary PMR. There is a lack of robust evidence for the use of DMARDs in patients with ICI-induced PMR. Methotrexate is the DMARD of choice, with doses similar to those given for arthritis. With respect to biologic DMARDs, tocilizumab is an effective therapy for giant cell arteritis which is often associated with primary PMR. It could therefore be potentially effective in the ICI-induced setting. Other biologic DMARDs have not been proven to be efficacious for primary PMR or giant cell arteritis.

Patients with suspected giant cell arteritis require immediate higher dose corticosteroids to avoid vascular occlusion.

Re-initiation of ICI therapy may be difficult as patients may have persistent symptoms even after discontinuation. Re-challenging is possible as PMR is not life threatening. However, in patients with associated giant cell arteritis, ICIs should be permanently withheld.

Myositis

Epidemiology

Myositis is a rare, but life-threatening IrAE. It has been reported with all ICIs, but appears to occur more frequently in those patients receiving combination immunotherapy. The incidence of myositis cannot be adequately established with the available data, but the frequency reported has ranged from < 1% to 6 % of ICI-treated patients [41-43, 53, 71]. It tends to occur early during therapy, sometimes after a single dose [72].

Clinical Manifestations

Onset is generally acute, with patients developing severe weakness, with difficulty standing up, getting out of bed, walking, and raising their arms [55, 72, 73]. They can also report myalgia. Proximal muscle strength is significantly decreased. When severe, patients can develop hoarseness, dysphagia shortness of breath, and even respiratory failure. A few patients, especially those receiving combination therapy, may develop severe necrotizing myositis with rhabdomyolysis, which can be suspected if their urine is dark, and requires prompt management.

As discussed in the previous section, myositis can also present in association with a myasthenia gravis-like syndrome with profound weakness [74]. Increasingly, there have been reports of patients developing severe myositis, myocarditis and myasthenic manifestations with a rapidly progressive course, which can be fatal. This triad has been observed more frequently in patients receiving combination immunotherapy with PD-1 blockade and ipilimumab [75-77].

While dermatomyositis has been classically described as a paraneoplastic syndrome, most patients with ICI-induced myositis do not have similar clinical or diagnostic features, suggesting that the mechanism of ICI-induced myositis is distinct from that of paraneoplastic myositis.

Diagnosis

Myositis can be life threatening and needs to be promptly diagnosed. Physical examination should include a full rheumatologic and neurologic exam with evaluation of strength for major muscle groups [24,46,49]. Laboratory testing should include serum CK, which is generally highly elevated, in the 1000's, and should be used for monitoring response to therapy. Other enzymes including aldolase, transaminases and lactate dehydrogenase are also elevated, but CK is more specific for muscle and is used for monitoring. Autoimmune serologies include myositis autoantibodies, as well as paraneoplastic neurologic antibodies. Anti-methylglutaryl-coenzyme A reductase (anti- HMG-CoA) antibodies can be requested in patients who have received concomitant statins. Myositis antibodies are generally negative. Patients with combined myasthenic manifestations, may have positive anti-striated muscle antibodies, and anti-acetylcholine receptor antibodies. Troponin levels should be evaluated in all patients, as myocarditis can be fatal if not promptly managed. Inflammatory markers may be useful in assessing response to treatment, but the most important laboratory parameters for monitoring treatment course are CK and troponin if myocarditis is present.

Electromyography and nerve conduction studies are useful to differentiate between myopathic and neurologic causes of weakness and results can be quickly obtained.

Muscle biopsy is not always necessary for management, but may be indicated when there is diagnostic uncertainty, or in cases which do not respond to therapy.

Magnetic resonance imaging can be useful when biopsies are not possible to evaluate muscle edema and can also assist in identifying the best site for biopsy.

Recommendations

Consultations with rheumatology and neurology should be initiated as soon as myositis is suspected. Cardiology should be consulted if there is evidence of myocardial involvement. Myositis rarely presents as a grade 1 or 2 adverse event as it is almost universally very debilitating. Checkpoint inhibitors should be permanently discontinued in most cases. Many patients will require hospitalization given the acute, rapidly progressing presentation of myositis.

Treatment will be based on the clinical evaluation and CK levels. For grade 3 cases, therapy with corticosteroids can be oral at 1mg/kg/day prednisone or equivalent, but should be escalated if there is no response or deterioration within days according to clinician judgment.

For patients with severe symptoms such as dysphagia, shortness of breath, or severe impairment in mobility, intravenous corticosteroids should be started at 2mg/kg/day. Given the potential for serious complications, response to therapy should be evaluated daily, and for patients who do not respond plasmapheresis should be considered. IVIg therapy is a therapeutic option, but the onset of therapeutic effect is longer than for plasmapheresis.

Other DMARD treatments may be considered if there are challenges in lowering the corticosteroid dose. Synthetic DMARDs used for myositis include methotrexate, azathioprine and mycophenolate mofetil. Biologic DMARDs used in ICI-induced myositis are rituximab, an anti-CD20 chimeric monoclonal antibody, and the TNF-alpha inhibitor, infliximab.

Patients with rhabdomyolysis should be adequately hydrated with intravenous fluids to avoid renal complications.

General considerations in the management of rheumatic IrAEs

Rheumatic IrAEs greatly impair patients' quality of life as they can cause severe pain, and limitations in mobility that interferes with the activities of daily living. Myositis is the most severe of the rheumatic IrAEs. It can be fatal and can occur after

a single ICI dose. To date, no risk factors or biomarkers have been identified that predict those who may be susceptible to this immune toxicity, or how to promptly diagnose it before the development widespread muscle necrosis or myocarditis.

Of interest, ICI-induced arthritis and PMR are somewhat different from IrAEs in other organs as they can occur after many months of treatment in patients who have not had other IrAEs and may be challenging to manage. These complications are often associated with long-lasting persistent symptoms and inflammatory features, even after discontinuation of ICI therapy. In this context, there are reports of patients who have required up to 2 years of DMARD treatment.

Because there is a lack of evidence on the management of rheumatic IrAEs, guidance is provided by expert recommendations or empirical treatments. Overall, management principles are similar for most rheumatic IrAEs. Mild events can be adequately treated with low-dose steroids, and ICI therapy can be continued if patients respond to treatment of the IrAE. For more severe cases, prompt initiation with DMARDs is indicated if steroids cannot be tapered.

Risk-benefit considerations are crucial in establishing best practices. The ultimate goal of IrAE management is to avoid life-threatening complications, improve symptom burden and quality of life, and limit therapies and actions, such as persistent immunosuppression that may promote cancer progression. In these settings, a personalized multidisciplinary approach is needed to effectively manage these complications.

Immune mediated Renal Toxicities

Both CTLA-4- and PD-1-targeted checkpoint mechanisms have been shown to play an important role in limiting renal injury in several experimental models [78]. The incidence of any grade acute kidney injury (AKI) due to immune-mediated toxicity is between 1.4 and 2.2% and between 0 and 0.9% grade 3–4 AKI when patients were treated with single agent CPI. The incidence is higher for combination checkpoint inhibition with all-grade toxicity of 4.9% and grades 3–4 of 1.7% [79]. Combination therapy also carries a higher risk of AKI due to non-immune-mediated toxicity [80].

Alongside numerous case reports, several case series have been published describing renal immune-mediated toxicities [79, 81,82,83,84]. Most patients develop acute interstitial nephritis (AIN) with predominantly CD3-positive T cell lymphocytic infiltration of the tubular-interstitial compartment. However, as with other immune-mediated toxicities, a broad range of inflammatory renal pathologies has been described.

Several types of glomerular lesions have been reported in association with checkpoint therapy. Minimal change disease (MCD) is the most frequent, followed by IgA glomerulonephropathy, pauci-immune glomerulonephritis, and membranous nephropathy [82, 83]. Vasculitis has also been described, occasionally with presence of serum anti-neutrophil cytoplasmic antibodies (ANCA) [83]. Most patients with AIN present with AKI. In a case series, 14 patients with biopsy-proven renal immune-mediated toxicity, 6 patients had grade 3 or higher AKI [84], while in another series 11 out of 13 patients had at least grade 3 toxicity [79]. Although AIN has been associated with active urinary sediment with WBCs and WBCs casts, many patients with immune-mediated toxicity had bland urine [79, 84]. Some patients with MCD or membranous nephropathy had no AKI and presented with nephrotic syndrome.

Patients with cancer are at high risk of AKI due to dehydration, sepsis, contrast nephropathy, other concomitant nephrotoxic medication, and intra-abdominal disease causing obstructive uropathy. In one case series of 12 patients who developed AKI while treated with checkpoint inhibitors, 5 patients had non-specific, non-immune-mediated acute tubular injury. Diagnosis of other etiologies of AKI may prevent unnecessary discontinuation of checkpoint inhibitors and minimize exposure to corticosteroids. Renal biopsy should be reserved for those patients in whom the etiology of the AKI is unclear or have steroid-refractory renal disease [24].

In patients treated with checkpoint inhibitors who develop AKI, there should be a high suspicion of immune-mediated pathology unless an alternative etiology is apparent. AKI developed at a median of 14 weeks after the last ICI dose [85]. These patients should be commenced on 0.5–1 mg/kg of oral corticosteroids. Corticosteroids should be titrated according to clinical response and should be weaned off slowly. If there is no improvement, or if there is further deterioration in

renal function despite oral treatment, corticosteroid treatment should be escalated to intravenous corticosteroids at 1–2 mg/kg.

Immunosuppressive agents, such as mycophenolate mofetil or infliximab, should be considered in patients with refractory immune-mediated renal toxicity [24, 83]. A small number of patients will experience a relapse of their immune-mediated renal toxicity on reducing the dose of corticosteroid and should also be commenced on immunosuppression to aid steroid weaning. These recommendations for management are summarized in Table 3. In addition, the time of onset of cardiovascular, rheumatic, and renal-related IrAEs in relationship to other IrAEs [7, 20, 64] is depicted in Fig. 1.

Table 3: Management of Renal IrAE's

Nephritis		
Investigations	**Urinalysis and Urinary Casts** **Albumin Creatinine Ratio** **USS kidneys/bladder** **Autoantibodies**	**Consider renal biopsy**
Management	**Oral Prednisolone 1mg/kg** **Supportive renal treatment – IV fluids**	**IV Corticosteroids (1-2mg/kg)** **Supportive renal treatment – IV fluids** **Infliximab/MMF if refractory to steroids**

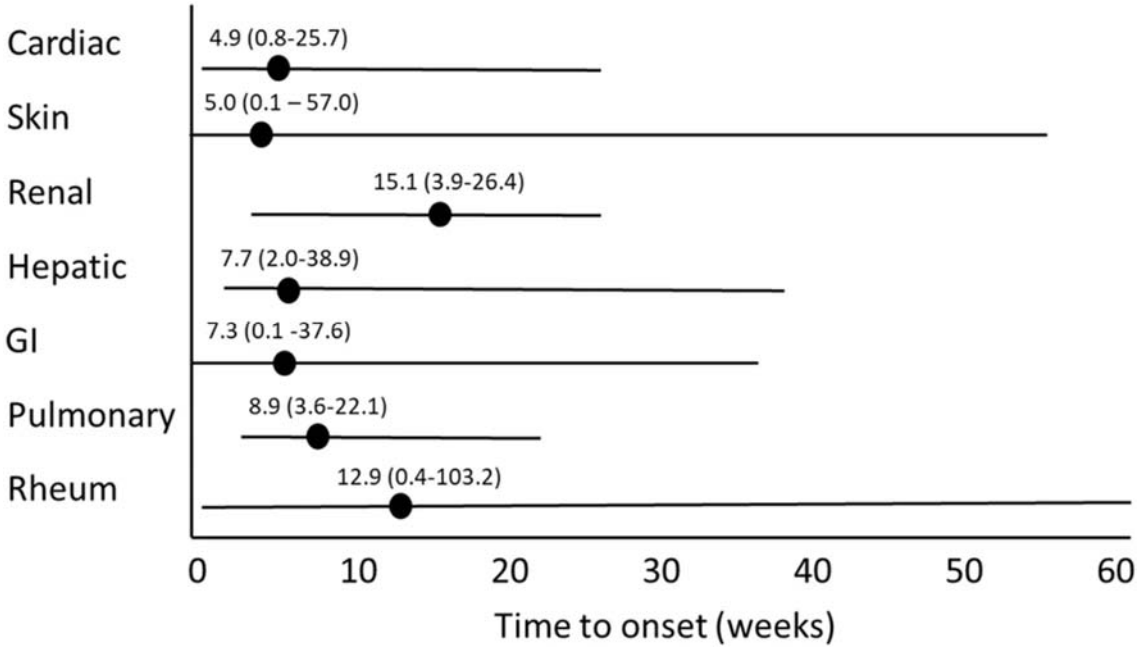

Fig. 1. Time (average, range) in weeks following start of anti-PD-1 monotherapy to toxicity by different organ systems

Conclusion

The clinical work-up and management of patients with immune-mediated cardiovascular, rheumatic and renal toxicities is complex and evolving. These state-of-the-art MASCC recommendations provide a comprehensive overview of management, but will require continuing revision as further research and randomized clinical trials are needed.

Conflict of interest

AW, XP, AB, RA, JC, TC, PG, DG RAG and VRS have no conflict of interest to declare. MD reports grants from Novartis, other (SAB) from Neoleukin Therapeutics, personal fees from Partner Therapeutics, personal fees from Tillotts Pharma, grants from Genentech, outside the submitted work. MG reports consultant work with Bristol Myers Squibb (BMS), and AstraZeneca, outside the submitted work. IG reports other (Stock Ownership) from Pfizer Inc., personal fees from CytomX Inc, outside the submitted work. DBJ reports other (advisory board) from Array Biopharma, grants and other (advisory board) from BMS, other (advisory board) from Jansen, grants from Incyte, other (advisory board) from Merck, other (advisory board) from Novartis, outside the submitted work. In addition, DBJ has a patent Co-inventor on use of CTLA-4 agonist for IAEs pending. BLR reports personal fees and other (advisory board) from Merck and Co, grants, personal fees and other (advisory board) from BMS, grants, personal fees and other (advisory board) from Roche South Africa, personal fees and other (advisory board) from AstraZeneca, during the conduct of the study. MSA reports personal fees from Gilead, grants from Pfizer, personal fees from Abbvie, outside the submitted work.

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