Rheumatologic complications of checkpoint inhibitor immunotherapy: a review

Ezzi MS, Kubo MN

Abstract

Background: Immune Checkpoint Inhibitors (ICIs) are currently used in the management of various cancers. However, they tend to cause adverse effects, collectively known as immune related adverse effects, (irAEs)by causing tissue damage due to immune activation.
Objective: The aim of this literature review is to address those rheumatological irAEs associated with the use of ICIs and how to manage them.
Data source: The literature review uses medical science-based literature published locally and internationally on the risk of rheumatological immune related adverse effects.
Conclusion: A spectrum of rheumatological irAEs have been linked to the treatment of various malignancies with ICIs, the most common being inflammatory arthritis. Most rheumatological irAEs can be managed successfully by use of glucocorticoids

Key words: Immune checkpoint inhibitors, Immunotherapy, Rheumatology, Arthritis, Glucocorticoids, Immune related adverse effects

Department of Clinical Medicine and Therapeutics, School of Medicine, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202, Nairobi, Kenya

Corresponding author
Dr Mohammed S Ezzi.
Email: mezzi@uonbi.ac.ke

Introduction

Immune checkpoint inhibitors are a type of immunotherapy that is currently being used in the management of various types of cancers. However, they cause a myriad of adverse effects involving nearly every organ system. These adverse effects are collectively known as immune-related adverse events (irAEs). The irAEs result from tissue damage by immune activation and inflammation.

The ICIs work by blocking inhibitory molecules on T cells and tumour cells. By doing so, they enhance T cell mediated immune response towards cancer cells, leading to cancer cell death. Initially ICIs effectiveness was demonstrated in metastatic melanoma, but many indications have since been approved, including non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma and many other solid tumours. In this article, we review the rheumatologic complications of ICIs and their management.

Mechanism of action of ICIs

Usually, when a T cell is activated, multiple mechanisms regulate the level of activation preventing over activation of the T cell response. Tumour cells overly express these inhibitory molecules dampening and evading the immune system[1]. The major pathways that control T cell activation are binding of cytotoxic lymphocyte antigen protein 4 (CTLA-4) on T cells to CD80/86 on antigen presenting cell, and binding of programmed cell death receptor 1 (PD-1) to programmed cell death ligand 1 or 2 (PD-L1 or PD-L2). ICIs block these inhibitory pathways, allowing for increased activation of T cell with a greater response against tumours.

The first approved ICI, ipilimumab, blocks the binding of CTLA-4 to CD80/86. Other ICIs inhibit either PD-1 or PD-L1. The PD-1 inhibitors include pembrolizumab, nivolumab and cemiplimab while the PD-L1 inhibitors include atezolizumab, avelumab and durvalumab (Figure 1).

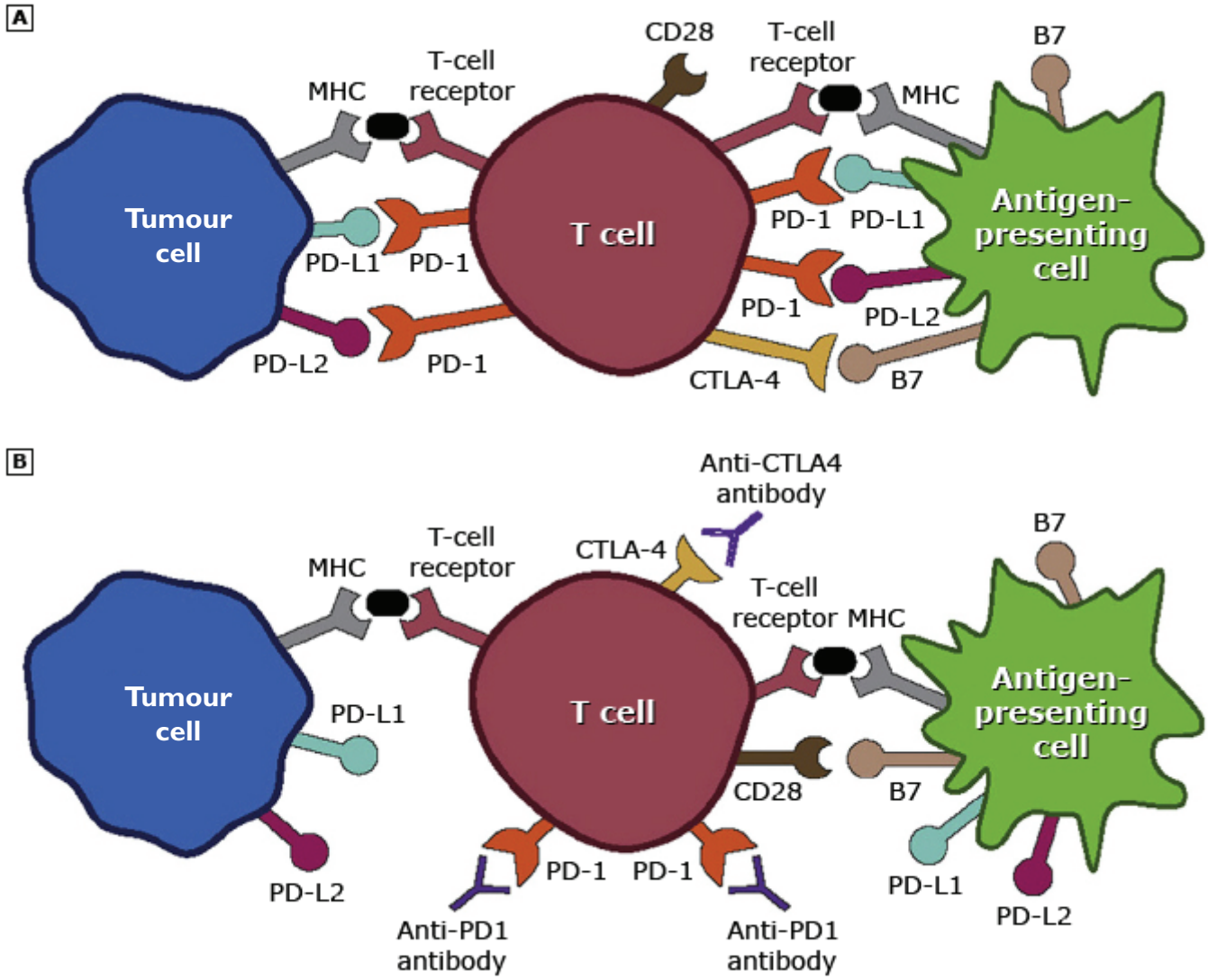
Pathogenesis of rheumatologic complications

ICIs can cause off-target tissue damage (irAEs) by non-specific activation of T cells. The clinical manifestations depend on the organ system involved, its severity and temporal relationship to ICI therapy[2].

The specific immune pathways implicated in irAEs are not yet determined. However, some data suggest that interleukin 17 and T-helper 17 (TH17) cell response may be responsible for the pathogenesis of irAEs[3].

There could be possible overlap in the pathogenesis of rheumatologic irAEs and rheumatoid arthritis. For example, abatacept which is fusion protein between CTLA-4 and Fc portion of IgG is used in the treatment of inflammatory arthritis. Its mechanism can be thought of as the converse of ipilimumab in that it blocks

Figure 1: A) PD-L1 and PD-L2 on tumour cells and APCs bind to PD-1 on the T cell, and B7 on APCs binds to CTLA-4 on the T cell.
(B) Antibodies to PD-1 or CTLA-4 block inhibitory interactions, allowing for positive costimulation (B7 binds CD28).



CTLA-4: cytotoxic lymphocyte antigen protein 4; PD-1: programmed cell death receptor 1; MHC: major histocompatibility complex; CD28: cluster of differentiation 28; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; APCs: antigen-presenting cells.

the activating interaction between CD28 and CD80/86, rather than blocking the inhibitory interaction[4]. Similarly, some mouse and human studies have implicated PD-1 in the pathogenesis of RA[5].

Epidemiology

The rheumatologic irAEs have been less reported in literature in comparison with other types of irAEs. The most common symptoms include arthralgia, myalgia and sicca complex[6]. The epidemiological estimates vary from 1% to 43% for arthralgia, 2% to 20% for myalgia and 3% to 24% for sicca syndrome[7]. However, the development of systemic autoimmune disease that requires rheumatological referral is less common, occurring in about 3.5% to 6.6% of the patients[8,9]. It is possible that the relatively low frequency rheumatologic irAEs is the result of failure to recognize the significance of rheumatologic disease symptoms by the treating provider, coupled with the fact that rheumatologic irAEs are rarely life-threatening and hence not graded as severe. Furthermore, it is unclear on how arthralgias actually represent inflammatory arthritis because of the different ways a given clinical symptom or finding may be coded (e.g., arthralgia, joint effusion, arthritis) for data collection. Most information of rheumatologic irAEs is from case reports.

The rheumatologic irAEs that occur include inflammatory arthritis, inflammatory myositis, sicca syndrome, vasculitis, eosinophilic fasciitis, polymyalgia

rheumatica, sarcoidosis and scleroderma[7,10-15]. The rheumatologic irAEs tend to occur more frequently in patients who are treated with ICI combination therapy and with anti-PD1/ ant-PDL1 as compared with monotherapy and anti-CTLA4 respectively[16]. In addition, 71% of patients with pre-existing autoimmune disease may experience flares or develop another autoimmune disease[17].

General principles of management

The clinical manifestation of rheumatologic irAEs varies widely. Some clinical manifestation may mirror classic rheumatological diseases while for others, the characteristic features may be absent. In addition, it is common for patients with rheumatologic irAEs to have other non-rheumatologic irAEs, hence obtaining a detailed history and thorough physical examination is important. The severity of irAEs, future cancer treatment options, tumour response, oncologist and patients' preference should all be considered in deciding treatment for the rheumatologic irAEs. It is recommended that there should be close consultation with the patient's oncologist, to determine the most appropriate intervention and whether to continue or discontinue ICI therapy.

Inflammatory arthritis

Clinical manifestation and diagnosis

Inflammatory arthritis is the most common rheumatological irAE[18,19]. It usually develops within two weeks but may be delayed up to a year of ICI initiation with joint damage occurring within months of symptom onset[9,19]. Inflammatory arthritis presents with a variety of clinical presentations ranging from small joint polyarthritis to large joint oligoarthritis to psoriatic arthritis[18,20,21]. Patients treated with anti-PD1 and anti-PDL1 are more likely to develop small joint polyarthritis as the only irAE, while those treated with anti-CTLA4 will develop large joint oligoarthritis and have had another irAE[22].

The diagnosis is primarily made clinically, based upon the history and physical examination finding of a new onset arthritis following treatment with ICI. A detailed history should be taken to rule out antecedent rheumatological manifestations and the pattern of joint involvement should be characterized. A diagnosis of ICI induced arthritis can be made in patients who do not have preceding symptoms and presence of features suggestive of classic form of inflammatory arthritis.

Laboratory studies are useful but are not necessary for diagnosis. Most patients are seronegative for rheumatoid factor and cyclic citrullinated peptide. Inflammatory surrogate markers like C-reactive protein and erythrocyte sedimentation rate may be elevated, but their utility is compromised, as these markers are also elevated in malignancy.

Plain radiographs of the affected joint should be taken at time of initial presentation more so to serve as a baseline for comparison with later studies as they may be normal during the early phase of the disease. Magnetic resonance imaging and ultrasound have shown tenosynovitis, enthesophytes and bony erosive disease[23]. This finding can be helpful in distinguishing inflammatory arthritis from non-inflammatory joint disease. Other disease conditions that present as inflammatory arthritis should be ruled out. These include paraneoplastic syndromes, polyarthralgia due to medications and bone metastasis with erosive joint changes. Bone metastasis should be suspected if there is a joint with disproportionate erosive disease or a joint that does not respond to therapy.

Treatment

Treatment of inflammatory arthritis due to an irAE is based upon case reports and case series. The treatment should be personalized based on the clinical findings and the severity of the disease. Treatment decision should be made in close collaboration with the patient's oncologist.

Treatment of mild arthritis

Mild arthritis is the involvement of few joints without any significant functional compromise. Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) or low dose glucocorticoids are recommended for patients with mild arthritis. ICI therapy is usually continued. Oral NSAIDs are commonly used but some patients with very mild arthritis may also benefit from topical NSAID. There is no preference for any specific NSAID, however the drugs should be used at the lowest necessary dose and for the shortest duration needed. Patients should be monitored regularly for gastrointestinal adverse effects as ICI therapy has also been associated with gastrointestinal adverse effects like diarrhoea and colitis.

In patients whom NSAID are contraindicated or in whom a more rapid response is required, glucocorticoids like prednisone can be used. Treatment should be initiated with the lowest possible dose of glucocorticoid, for example prednisone 10mg to 20mg daily. The response should be assessed after couple of weeks and the dose adjusted to the minimal dose required for disease control. ICI therapy can be safely used concurrently with low dose glucocorticoids. Intraarticular steroid injection, similar to rheumatoid arthritis, can be administered in patients with oligoarticular disease[24].

Treatment of moderate and severe arthritis

Moderate and severe arthritis is involvement of multiple joints or functional impairment. In these patients' higher doses of glucocorticoids, for example prednisone 1mg/kg/day, may be required. ICI therapy is withheld temporarily. High doses of glucocorticoids should at least be used for a month and then tapered down to a lower dose if the

patient is responding well to therapy. ICI therapy can be re-initiated during the period of glucocorticoid tapering.

Conventional Disease-Modifying Antirheumatic Drugs (DMARDs) can be used in patients who cannot be successfully weaned off to a lower dose or entirely off glucocorticoids. These include sulfasalazine, hydroxychloroquine or methotrexate. They should be initiated in the same way as for rheumatoid arthritis[18,19]. The decision to start ICI therapy should be made on an individual basis.

In selected patients with severe arthritis who have steroid refractory disease, the use of Tumour Necrosis Factor (TNF) inhibitors has been suggested or preferred. These include patients in whom it would be undesirable to wait for several weeks for a response with conventional DMARD, or in patients in whom synthetic DMARDs is contraindicated like patients with liver disease or cytopenia. Either of the TNF inhibitors: infliximab, adalimumab and etanercept can be used. There is no preference for one over another. The precautions, dosing and strategies used for these agents is similar to those used in patients with RA and other related conditions[18,19].

The efficacy and safety of other drugs like tocilizumab is extremely limited. Tocilizumab has been used in small number of patients to treat inflammatory arthritis[25]. It is mostly recommended in patients who have contraindications to TNF inhibitors or who do not respond to with at least two months treatment of TNF inhibitors. There have been concerns about using concurrent tocilizumab and ICI, as both of these drugs increase the risk of colitis and intestinal perforation, however limited data suggests no such increased risk[26,27].

Prognosis

The development and treatment of ICI associated inflammatory arthritis does not adversely affect the tumour prognosis[28-30]. However, the arthritis may persist following discontinuation of ICI[31].

There is a theoretical concern that immunosuppressive drugs used in the management of inflammatory arthritis may impair the effectiveness of ICI. However, albeit limited data, there has been no evidence to suggest that immunosuppressive treatment dampen the effectiveness of ICI[31,32].

Sicca syndrome and other ocular diseases

Xerostomia and keratoconjunctivitis sicca that resemble Sjogren's syndrome have been reported in patients treated with ICI[18]. They usually occur abruptly within the first three months of treatment. Xerostomia usually predominates while parotid swelling and parotitis occurs rarely. Most patients are seronegative for autoantibodies to Ro/SSA and La/SSB[33].

ICI has also been associated with other forms of ocular inflammation like uveitis and peripheral ulcerative keratitis[34]. Salivary gland biopsies show a varied histopathologic findings ranging from histopathology finding similar to Sjogren syndrome to diffuse T cell lymphocytic infiltration with acinar injury[33].

Management

Management of ICI induced sicca syndrome is similar to that of primary Sjogren's syndrome. Dental care with saliva substitutes and sialagogues is important in patients with xerostomia. Parotid gland swelling and/or parotitis is usually managed by giving prednisone (10mg – 40mg) tapered off over weeks.

The treatment of severe oral adverse effects involves discontinuation or temporarily withholding ICI, use of moderate to high doses of prednisone, diet restriction to purees and use of oral lubricants. The patient should also be referred to an oral medicine specialist. ICI can be reinitiated after at least three months following successful glucocorticoid taper[33].

Artificial tears should be prescribed to patients with ICI associated dry eyes. Furthermore, the patients should avoid other medications that cause dryness of the eyes. Patients with severe or refractory symptoms should be referred to an ophthalmologist.

Polymyalgia rheumatica/giant cell (temporal) arteritis

Clinical features and diagnosis

Polymyalgia Rheumatica (PMR) and Giant Cell Arteritis (GCA) are rare rheumatological irAE. They can occur in isolation or in combination. The median time of onset is three months after initiation of ICI. Similarly, to non-ICI PMR and/or GCA, the patients are elderly with a median age of about 57 years[35,36]. The clinical presentation of PMR is similar to those patients who have not received ICI.

A prompt temporal artery biopsy should be done to confirm the diagnosis in patients in whom GCA is suspected. The biopsy finding is similar to non-ICI GCA. Surrogate inflammatory markers like C-Reactive Protein(CRP) and Erythrocyte Sedimentation Rate (ESR) may be elevated due to malignancy and may not be useful for diagnosis. However, if CRP and ESR are normal, then GCA is very unlikely.

The role of imaging has not been well characterized. However, an ultrasound or MRI may be useful to support a PMR diagnosis if bursitis or tendinitis is seen in the classic areas and in patients who have PMR like symptoms with normal levels of inflammatory markers.

Treatment

The treatment for GCA and PMR is similar to that in patients without ICI therapy. Glucocorticoids are the mainstay of treatment. Higher doses of glucocorticoids may be required in GCA than with PMR[14]. The higher

doses of glucocorticoids used for the treatment of GCA requires withholding or discontinuation of ICI, while in PMR, due to the lower doses used, ICI may not be discontinued. The role of biologic agents like tocilizumab is unclear[36].

Inflammatory myopathies

Dermatomyositis and polymyositis are uncommon irAEs of ICI therapy[11,37]. Most patients present with proximal myopathy, similar to the classic form of the disease, but there have been a few reported cases of respiratory muscle and facial muscle involvement[38,39]. In addition, some patients may have concomitant myasthenia gravis and/or myocarditis[40,41].

The diagnosis is based on physical examination and elevated muscle enzymes supplemented by either an electromyography or muscle MRI. The role of muscle biopsy is unclear because of different histopathological patterns[11,39,42].

Glucocorticoids are the mainstay of treatment ranging from 30mg prednisone daily to 1000mg methylprednisolone. This is followed by gradual dose tapering[11,37]. Intravenous Immune Globulin (IVIG) can be used in patients with severe myopathy, respiratory distress and/or concomitant myasthenia gravis[43]. ICI should be discontinued in all cases and it is unclear whether the patients can be safely rechallenged with ICI.

Other rheumatologic irAEs

These irAEs occur infrequently and literature review contains mostly of case reports and/or series. They include Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis[44], eosinophilic fasciitis[13], systemic sclerosis[15], digital ischemia[45], and single organ vasculitis[12,46]. The optimum treatment approaches have not been determined for these irAEs, and the treatment recommendations for the classic forms should be followed. The treatment options should be discussed in collaboration with the rheumatologist, oncologist and the patient.

It is important to note, that there may be other unreported rheumatologic irAEs. Hence a careful history of cancer therapies should be taken for patients presenting with rheumatological symptoms and history of cancer.

Pre-existing rheumatological diseases

There is limited data on the efficacy and safety of ICI therapy in patients with pre-existing rheumatological diseases as these patients have been excluded from clinical trials evaluating immunotherapy due to concerns about exacerbation of underlying disease and/or irAE[47]. However, some observational studies suggest that most of these patients can safely receive ICI[17,48]. About a third of patients with pre-existing rheumatological disease have experienced flares when started on ICI treatment[49]. Most of these have been successfully managed with the use of glucocorticoids but some have required discontinuation of the ICI therapy[50]. Severe flares may require treatment with other biologic agents like TNF inhibitors.

Patients with established rheumatological diseases who are on ICI therapy should be closely monitored by their rheumatologist and oncologist. The effect of DMARDs on immunotherapy is unclear, however hydroxychloroquine, sulfasalazine and low dose glucocorticoids can be safely used concurrently with ICI.

Conclusions

A spectrum of rheumatological irAEs can occur as a result ICI treatment. The most common being inflammatory arthritis. The precise epidemiology is not known. Several factors, namely the severity of irAE, tumour response, relative risk and benefits of both rheumatologic and oncologic treatment options and patients' preference, should be considered before determining the management approach. Most rheumatological irAEs can be managed successfully by use of glucocorticoids, the dose and duration depending on the severity of the irAE. Severe irAE may require temporary withholding or discontinuation of ICI and use of other biological agents like TNF inhibitors. Patients with preexisting rheumatological disease can safely use ICI albeit a risk of disease flare up.

References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; **12**(4):252–264.
2. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* 2012; **30** (21):2691–97.
3. Lord JD, Hackman RC, Moklebust A, Thompson JA, Higano CS, *et al.* Refractory colitis following anti-CTLA4 antibody therapy: analysis of mucosal FOXP3+ T cells. *Dig Dis Sci.* 2010; **55** (5):1396–405.
4. Ceeraz S, Nowak EC, Burns CM, Noelle RJ. Immune checkpoint receptors in regulating immune reactivity in rheumatic disease. *Arthritis Res Ther.* 2014; **16**(5). doi: 10.1186/s13075-014-0469-1.
5. Raptopoulou AP, Bertsias G, Makrygiannakis D, Verginis P, Kritikos I, *et al.* The programmed death 1/programmed death ligand 1 inhibitory pathway is up-regulated in rheumatoid synovium and regulates peripheral T cell responses in human and murine arthritis. *Arthritis Rheum.* 2010; **62**(7):1870–80.
6. Benfaremo D, Manfredi L, Luchetti MM, Gabrielli A. Musculoskeletal and rheumatic diseases induced by immune checkpoint inhibitors: a review of the literature. *Curr Drug Saf.* 2018; **13**(3):150–164.
7. Cappelli LC, Gutierrez AK, Bingham CO, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature. *Arthritis Care Res* (Hoboken). 2017; **69**(11):1751–63.

8. Lidar M, Giat E, Garelick D, Horowitz Y, Amital H, *et al.* Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. *Autoimmun Rev.* 2018; **17**(3):284–289.
9. Kostine M, Rouxel L, Barnetche T, Veillon R, Martin F, *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):393–398.
10. Chan MMK, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. *J Immunother.* 2015; **38**(1):37–39.
11. Hunter G, Voll C, Robinson CA. Autoimmune inflammatory myopathy after treatment with ipilimumab. *Can J Neurol Sci.* 2009; **36**(4):518–520.
12. Minor DR, Bunker SR, Doyle J. Lymphocytic vasculitis of the uterus in a patient with melanoma receiving ipilimumab. *J Clin Oncol.* 2013; **31**(20): e356-e356.
13. Khoja L, Maurice C, Chappell M, Macmillan L, Al-Habeeb AS, *et al.* Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma. *Cancer Immunol Res*. 2016; **4**(3):175–178.
14. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. *Arthritis Rheumatol* (Hoboken, NJ). 2014; **66**(3):768–769.
15. Barbosa NS, Wetter DA, Wieland CN, Shenoy NK, Markovic SN, Thanarajasingam U. Scleroderma Induced by Pembrolizumab: A Case Series. *Mayo Clin Proc.* 2017; **92**(7):1158–63.
16. Allenbach Y, Anquetil C, Manouchehri A, Benveniste O, Lambotte O, *et al.* Immune checkpoint inhibitor-induced myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities. *Autoimmun Rev.* 2020; **19**(8).doi:10.1016/j.autrev.2020.102586.
17. Tison A, Quéré G, Misery L, Funck-Brentano E, Danlos FX, *et al.* Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: a nationwide, multicenter cohort study. *Arthritis Rheumatol* (Hoboken, NJ). 2019; **71**(12):2100–11.
18. Cappelli LC, Gutierrez AK, Baer AN, Albayda J, Manno RL, *et al.* Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis.* 2017; **76**(1):43–50.
19. Calabrese C, Kirchner E, Kontzias K, Velcheti V, Calabrese LH. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open*. 2017; **3**(1). doi:10.1136/rmdopen-2016-000412.
20. Belkhir R, Le Burel S, Dunogeant L, Marabelle A, Hollebecque A, Besse B, *et al.* Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann Rheum Dis.* 2017; **76**(10):1747–50.
21. Law-Ping-Man S, Martin A, Briens E, Tisseau L, Safa G. Psoriasis and psoriatic arthritis induced by nivolumab in a patient with advanced lung cancer. *Rheumatology* (Oxford). 2016; **55**(11):2087–89.
22. Cappelli LC, Brahmer JR, Forde PM, Le DT, Lipson EJ, Naidoo J, *et al.* Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. *Semin Arthritis Rheum.* 2018; **48**(3):553–557.
23. Albayda J, Dein E, Shah AA, Bingham CO, Cappelli L. Sonographic findings in inflammatory arthritis secondary to immune checkpoint inhibition: a case series. *ACR Open Rheumatol. 2*019; **1**(5):303–307.
24. Naidoo J, Cappelli LC, Forde PM, Marrone KA, Lipson EJ, *et al.* Inflammatory arthritis: a newly recognized adverse event of immune checkpoint blockade. *Oncologist.* 2017; **22**(6):627–630.
25. Kim ST, Tayar J, Trinh VA, Suarez-Almazor M, Garcia S, *et al.* Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheum Dis.* 2017; **76**(12):2061–64.
26. Dimitriou F, Hogan S, Menzies AM, Dummer R, Long G V. Interleukin-6 blockade for prophylaxis and management of immune-related adverse events in cancer immunotherapy. *Eur J Cancer.* 2021; **157**:214–224.
27. Campochiaro C, Farina N, Tomelleri A, Ferrara R, Lazzari C, *et al.* Tocilizumab for the treatment of immune-related adverse events: a systematic literature review and a multicentre case series. *Eur J Intern Med.* 2021; **93**:87–94.
28. Judd J, Zibelman M, Handorf E, O'Neill J, Ramamurthy C, *et al.* Immune-related adverse events as a biomarker in non-melanoma patients treated with programmed cell death 1 Inhibitors. *Oncologist.* 2017; **22**(10):1232–37.
29. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, *et al.* Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with Nivolumab: a prospective cohort study. *J Thorac Oncol.* 2017; **12**(12):1798–805.
30. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, *et al.* Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol.* 2018; **4**(3):374–378.
31. Braaten TJ, Brahmer JR, Forde PM, Le D, Lipson EJ, *et al.* Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. *Ann Rheum Dis.* 2020; **79**(3).doi:10.1136/annrheumdis-2019-216109.
32. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, *et al.* Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients

with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol.* 2015; **33**(28):3193–98.
33. Warner BM, Baer AN, Lipson EJ, Allen C, Hinrichs C, *et al.* Sicca syndrome associated with immune checkpoint inhibitor therapy. *Oncologist.* 2019; **24**(9):1259–69.
34. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. *Curr Opin Oncol.* 2016; **28**(4):288–294.
35. Micaily I, Chernoff M. An unknown reaction to pembrolizumab: giant cell arteritis. *Ann Oncol Off J Eur Soc Med Oncol.* 2017; **28**(10):2621–22.
36. Calabrese C, Cappelli LC, Kostine M, Kirchner E, Braaten T, Calabrese L. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. *RMD Open.* 2019; **5**(1).doi: 10.1136/rmdopen-2019-000906.
37. Ali SS, Goddard AL, Luke JJ, Donahue H, Todd DJ, *et al.* Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. *JAMA Dermatol.* 2015; **151**(2):195–199.
38. Yoshioka M, Kambe N, Yamamoto Y, Suehiro K, Matsue H. Case of respiratory discomfort due to myositis after administration of nivolumab. *J Dermatol.* 2015; **42**(10):1008–9.
39. John S, Antonia SJ, Rose TA, Seifert RP, Centeno BA, Wagner AS, *et al.* Progressive hypoventilation due to mixed CD8+ and CD4+ lymphocytic polymyositis following tremelimumab - durvalumab treatment. *J Immunother Cancer.* 2017; **5**(1).DOI: 10.1186/s40425-017-0258-x.
40. Chen JH, Lee KY, Hu CJ, Chung CC. Coexisting myasthenia gravis, myositis, and polyneuropathy induced by ipilimumab and nivolumab in a patient with non-small-cell lung cancer: A case report and literature review. *Medicine* (Baltimore). 2017; **96**(50).doi:10.1097/MD.0000000000009262.
41. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, *et al.* Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. *Neurology.* 2017; **89**(11):1127–34.
42. Matas-García A, Milisenda JC, Selva-O'Callaghan A, Prieto-González S, Padrosa J, *et al.* Emerging PD-1 and PD-1L inhibitors-associated myopathy with a characteristic histopathological pattern. *Autoimmun Rev.* 2020; **19**(2).doi:10.1016/j.autrev.2019.102455.
43. Diamanti L, Picca A, Bini P, Gastaldi M, Alfonsi E, *et al.* Characterization and management of neurological adverse events during immune-checkpoint inhibitors treatment: an Italian multicentric experience. *Neurol Sci.* 2022; **43**(3):2031–41.
44. Uner M, Alhasson B, Obhrai J, Bagnasco SM. ANCA-associated pauci-immune necrotizing glomerulonephritis during the treatment with pembrolizumab. *Virchows Arch.* 2021; **478**(4):801–804.
45. Gambichler T, Strutzmann S, Tannapfel A, Susok L. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. *BMC Cancer.* 2017; **17**(1):1–5.
46. Manusow JS, Khoja L, Pesin N, Joshua AM, Mandelcorn ED. Retinal vasculitis and ocular vitreous metastasis following complete response to PD-1 inhibition in a patient with metastatic cutaneous melanoma. *J Immunother Cancer.* 2014; **2**(1)doi:10.1186/s40425-014-0041-1.
47. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. 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):121–130.
48. Van der Kooij MK, Suijkerbuijk KPM, Aarts MJB, Van den Berkmortel FWPJ, Blank CU, *et al.* Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease: a cohort study. *Ann Intern Med.* 2021; **174**(5):641–648.
49. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, *et al.* Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol Off J Eur Soc Med Oncol.* 2017; **28**(2):368–376.
50. Lee B, Wong A, Kee D, Neeson P, Shackleton M, *et al.* The use of ipilimumab in patients with rheumatoid arthritis and metastatic melanoma. *Ann Oncol Off J Eur Soc Med Oncol.* 2016; **27**(6):1174–77.