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Treatment of immune checkpoint inhibitor-induced inflammatory arthritis

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Abstract

Purpose of review—This review summarizes the current evidence on treatment strategies for inflammatory arthritis because of cancer treatment with immune checkpoint inhibitors (ICI), prognosis of ICI-induced arthritis, and management of patients with preexisting inflammatory arthritis receiving ICI therapy.

Recent findings—Inflammatory arthritis is the most common rheumatic immune-related adverse event observed in patients receiving ICI therapy. Most patients can successfully be treated with low doses of corticosteroids or conventional synthetic disease modifying anti-rheumatic drugs (DMARDs). A small minority will develop severe symptoms requiring biologic therapy including TNF inhibitors and IL-6 receptor inhibitors. Many cases of inflammatory arthritis will resolve with cessation of ICI therapy. Some patients will develop persistent arthritis despite discontinuation. Patients with preexisting inflammatory arthritis (e.g. rheumatoid arthritis) commonly flare on ICI therapy, but can usually be managed with corticosteroids.

Summary—Inflammatory arthritis following ICI therapy for cancer is relatively common and the practicing rheumatologist should be able to recognize and manage it in conjunction with Oncology. The majority of patients respond to corticosteroids, but some will need treatment with conventional synthetic or biologic DMARDs. Additional studies should investigate the effects of immunosuppression on tumor response and the use of ICI therapy in patients with preexisting autoimmune disease.

Keywords

cancer; immune checkpoint inhibitor; inflammatory arthritis

INTRODUCTION

The emergence of immune checkpoint inhibitors (ICI) has revolutionized the treatment of cancer. Improved survival and prolonged responses are now being seen for previously difficult to treat malignancies [1–3]. ICIs primarily work by blocking inhibitory interactions

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between T cells and other cells and tissues, thus allowing for unchecked T-cell activation with resultant antitumor effect. The Food and Drug Administration (FDA) has approved to date seven ICIs for a myriad of malignancies, including for mismatch repair-related cancers regardless of origin, which represents the first tissue agnostic approval of an antineoplastic agent [4]. Currently approved ICIs target CTLA-4, PD-1, and PD-L1. Other checkpoint pathways are under investigation for development of targeted drugs include lymphocyte-associated gene 3 (LAG-3), T-cell immunoglobulin mucin 3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT) [5–7]. The consequence of generalized immune activation is inflammatory damage of healthy tissues, referred to as immune-related adverse events (irAE) [8▪▪]. The pathogenesis of irAEs is not fully characterized but is likely related to the effect of ICIs on T-cell activation and functioning [9–11]. Inflammatory arthritis is a well described complication from ICI therapy and estimates of incidence vary from 1 to 7% of patients treated [12▪]. Many more patient will suffer from arthralgias, up to 40% in some clinical trials [13]. Uniquely, whereas the vast majority of irAEs will resolve with holding treatment and glucocorticoids, inflammatory arthritis may persist despite these measures in a subset of patients [14▪].

The epidemiology and clinical presentation of inflammatory arthritis secondary to ICI therapy has previously been reviewed in this journal [15]. To summarize, multiple phenotypes of inflammatory arthritis have been reported in the literature and including small joint predominant polyarthritis similar to rheumatoid, large joint oligoarthritis frequently involving the lower extremities, tenosynovitis, psoriatic-type arthritis, and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) [15]. Patients treated anti-PD1 monotherapy are more likely to develop a small joint polyarthritis whereas patients treated with anti-CTLA4 therapy alone or in combination most commonly present with knee arthritis [16]. Inflammatory markers are variably elevated and the majority of patients will be seronegative for rheumatoid factor and anticitrullinated protein antibodies [16–19]. Imaging findings include Doppler-positive synovitis on ultrasound, joint effusions and synovitis on MRI, as well as erosions in severe cases [18]. Tendon involvement, with tenosynovitis and enthesitis, is also appreciated with musculoskeletal ultrasound [20,21]. This review will focus on current treatment strategies.

OVERARCHING PRINCIPLES

In managing patients with inflammatory arthritis, close collaboration with the treating oncologist is essential. According to the oncologic practice guideline for the management of immune-related adverse events (irAE), treatment should be dictated by the grade of the irAE. In oncologic practice, treatment-related side effects are classified on a scale of 1–5 [22–24,25▪]. In the context of inflammatory arthritis, grade 1 is defined as mild pain with erythema, inflammation, or joint swelling; grade 2 as moderate pain and limiting instrumental activities of daily living (ADLs), and grade 3 and 4 as severe pain resulting in irreversible joint damage and limiting self care ADLs. Most patients will experience grade 1 or 2 severity. Per oncologic guidelines, for grade 1 inflammatory arthritis, most patients will not be seen in a rheumatology practice as symptoms can be managed with analgesics, such as acetaminophen or NSAIDs and ICI therapy can be continued. If these conservative measures are not effective, or symptoms persist, rheumatology consultation is appropriate.

Additionally, grade 2 events and above should be referred to rheumatology for evaluation [23,24,25▪]. ICIs are not typically held unless events are grade 3 or higher. In patients who cannot perform ADLs, especially if they have already received a long course of ICIs, it is reasonable for rheumatologists to recommend holding the ICI to the oncologist.

INITIAL TREATMENT

The initial treatment strategy for patients with ICI-induced inflammatory arthritis should be NSAIDs for mild disease (grade 1) followed by glucocorticoids. In patients with limited large joint involvement, intra-articular glucocorticoids can be considered. This is in accordance with major oncologic society guidelines for management of rheumatic irAE [23,24,25▪]. The overwhelming majority of patients in case series of inflammatory arthritis are initially treated with glucocorticoids, likely because these patients developed severe enough arthritis to be referred to rheumatology. In our center's experience, for patients with moderate symptoms with impairments in instrumental ADLs, prednisone 10–20 mg daily is a reasonable starting dose of steroids. Patients with more severe arthritis and significant functional limitation may require doses of 40–60 mg daily initially with a plan to taper. In patients at risk for adverse effects from glucocorticoids or unable to taper below 10 mg of prednisone daily, we suggest initiating a conventional synthetic disease modifying anti-rheumatic drug (csDMARD), such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine, all of which have been used successfully in various case series [13,16,17,19]. There have been no comparative effectiveness studies assessing the response to these various agents and the choice should be guided by severity of arthritis and patient comorbidities.

BIOLOGICS

There are two scenarios where biologic therapies may be used. First, patients who have been treated with glucocorticoids and csDMARDs and who have persistent severe arthritis should be escalated to biologic therapy to prevent long-term joint damage and regain functional status. Second, patients where a faster time to arthritis improvement is needed may benefit initial treatment with a biologic therapy as a steroid-sparing agent. These may be patients in whom ICI therapy has been temporarily held because of toxicity with a subsequent plan to re-challenge or a patient with progressive cancer and a limited life span who wishes to achieve functional improvement to enjoy activities at the end of life. In our center's experience, patients typically note improvement after two to three doses of a subcutaneous TNF inhibitor for ICI-induced arthritis whereas response to csDMARDs tends to be slower.

Data with regard to biologic use in patients with ICI-induced inflammatory arthritis is limited to case reports and small case series. TNF inhibitors have been used with success in a number of case series [17,18]. Although small in size, previous studies have not found that treatment of inflammatory arthritis with either csDMARDs or TNF inhibitor impacts overall survival or progression of tumor [14▪,16] In melanoma, short courses of TNF inhibitors (one to two doses) had no effect on tumor response [26]. Beyond TNF inhibition, a case series of three patients with severe persistent arthritis demonstrated efficacy of IL-6 inhibition with tocilizumab [27]. All three patients demonstrated improvement in arthritis and one patient

maintained a durable tumor response from ICI therapy despite tocilizumab treatment and two of the three patients receiving concomitant ICI therapy and tocilizumab. In reports of treatment for inflammatory arthritis, ICIs are almost always held while biologics are administered. There is increasing interest about whether patients with severe arthritis and an indication for ongoing ICI therapy can be co-treated with ICIs and biologic therapies. In immune-related enterocolitis, one of the most frequent irAEs requiring discontinuation of ICI, a small case series of five patients demonstrated that colitis could successfully be treated with infliximab while continuing ICI therapy [28▪]. Patients demonstrated both clinical and pathologic improvement with regards to colitis and there was no cancer progression on restaging studies.

IMMUNOSUPPRESSION AND TUMOR RESPONSE

There are theoretical concerns that treating irAEs with immune-modulating agents will negatively affect tumor response to ICI therapy. The data from irAE treatment are mixed. Short-term glucocorticoid exposure has not been associated with attenuated antitumor efficacy in melanoma and other tumors [26,29,30]. Additionally, short-term TNF inhibition with one to two doses of infliximab did not negatively affect response to ipilimumab in melanoma [26]. Patients who receive high dose corticosteroids for hypophysitis, however, had a worsened overall survival than those who only received adrenal replacement-dosed corticosteroids [31]. Baseline immunosuppression may also be detrimental as those receiving prednisone 10 mg or higher had worsened response to anti-PD-1 and anti-PD-L1 agents for nonsmall cell lung cancer [32].

PERSISTENT ARTHRITIS

A recent study reported a significant percentage of patients will have a persistent arthritis despite cessation of ICI therapy. Of 41 patients with ICI-induced inflammatory arthritis followed longitudinally for at least 6 months, 20 patients had active arthritis at 6 months from ICI-discontinuation [14▪]. Patients with persistent arthritis were more like to have been treated with treated with combination immunotherapy and have experienced two or more irAEs versus those patients whose arthritis resolved. Those with persistent arthritis also had longer duration of ICI therapy. The results of this study suggest that patients receiving combination immunotherapy should undergo more frequent and prolonged monitoring. Interestingly, numerous studies across various malignancies have associated the development of an irAE with durable tumor response [30,33–36]. Similarly, in the afore-mentioned study on persistence of inflammatory arthritis, there was a nonsignificant trend toward better tumor responses in patients whose arthritis persisted.

OTHER CONSIDERATIONS

Good practice guidelines for patients with inflammatory arthritis should be extended to the treatment of ICI-induced inflammatory arthritis. Infection screening for chronic hepatitis and tuberculosis should be performed prior to starting immunosuppressive medication and may not have previously been completed as part of routine oncologic care. With regard to duration of treatment and tapering patients off immunosuppressive medications, there is no

data to guide management so treatment should be individualized to the patient. Many patients will experience an additional irAEs in conjunction with inflammatory arthritis, up to 40% in our center's experience [14▪]. In general, management decisions and monitoring response to therapy should be discussed with the treating oncologist and the relevant subspecialist.

PREEXISTING INFLAMMATORY ARTHRITIS

The preponderance of data suggests that patients with preexisting autoimmune disease including inflammatory arthritis receiving ICI therapy are likely to flare as a result of checkpoint inhibitors but that these flares can generally be managed. As these patients were excluded from clinical trials, the data is exclusively derived from retrospective cohort studies [37▪▪,38,39]. Early data from melanoma patients with preexisting autoimmune disease treated with anti-CTLA-4 therapy found that disease flares occurred relatively frequently (27% of patients) but could generally be managed with corticosteroids. Fifty percent of patients experienced neither a flare nor disease nor an irAE requiring treatment [40]. Similarly, treatment with PD-1-targeted therapy in patients with autoimmune disease resulted in flares in 38% of patients that again could be managed with immune suppression [41]. A study from the Mayo Clinic identified 16 patients with preexisting autoimmune disease prior to receiving ICI therapy out of 700 patients receiving ICI therapy from 2011 through 2016. Five of these patients had rheumatoid arthritis. Six out of 16 patients experienced an irAE; however, only one experienced a flare of their preexisting autoimmune disease [42]. In a multicenter case series from Australia, 10 out of 12 patients with patient receiving ICI-therapy experienced a flare of their disease, including four with inflammatory arthritis [43]. The largest study to date analyzed outcomes from ICI therapy in 112 patients in France with a preexisting autoimmune disease; 20 of the 112 patients had rheumatoid arthritis while the most common autoimmune disease was psoriasis. Only 24 of the patients were receiving any immunosuppression at the start of ICI treatment although 65% of these patients with rheumatoid arthritis (13 patients) were on immunosuppression. A flare of preexisting autoimmune disease and/or development of a separate irAE occurred in 71% of patients, with 47% of patient experiencing a flare of their preexisting autoimmune disease [44▪]. Immunosuppressive therapy was required in 43% of patients for management of flare and/or new irAE. Interesting, median progression free survival was shorter among patients receiving immunosuppression at start of ICI therapy compared with those who were not immunosuppressed (3.8 versus 12 months). The authors raise the question of whether immunosuppressive treatment of stable preexisting autoimmune disease should be discontinued prior to starting ICI therapy to maximize chance of tumor response. Although this is currently not the standard practice, this observation underscores the need for close and regular communication between the treating oncologist and rheumatologist in managing these patients. Additional research is needed to identify, which patients with preexisting rheumatic disease are at greatest risk for flare with ICI therapy and medical management prior to cancer therapy. There is no evidence currently supporting any particular immunomodulatory regimen for prophylaxis against flare or autoimmune disease.

CONCLUSION

Inflammatory arthritis secondary to ICIs is a well established clinical entity that rheumatologists should be familiar with in light of increasing use of these agents as first line therapy for a wide variety of malignancies. Although the presentation of inflammatory arthritis can vary, principles from the management of classic inflammatory arthritis may be applied. Initial treatment should consist of NSAIDs and glucocorticoids with a low threshold to start conventional synthetic DMARDs in patients with persistent arthritis and inability to taper steroids. Biologic therapy with TNF inhibitors is effective for refractory arthritis and does not appear to decrease antitumor effect of ICI therapy, although long-term studies of patients treated with these agents are needed. Patients with preexisting inflammatory arthritis are likely to experience a flare of their disease with initiation of ICI therapy; however, most cases can successfully be managed with the above treatment strategies and should not be an indication to withhold potentially lifesaving cancer treatment. As immunotherapy expands both in terms of the number of patients treated as well as the drug targets, more prospective research is needed to understand optimal management of patients both de novo inflammatory arthritis and those with preexisting autoimmune disease.

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KEY POINTS

- Immune checkpoint inhibitors (ICI) can cause a variety of immune-related adverse events, including inflammatory arthritis.
- Systemic corticosteroids are required for most patients referred to rheumatology for ICI-induced inflammatory arthritis; conventional synthetic DMARDs or biologic DMARDs may also be used.
- In limited studies, immunosuppression for ICI-induced inflammatory arthritis does not seem to affect tumor response negatively.
- Collaboration with the treating oncologist is critical for successful care of inflammatory arthritis because of ICIs.
- Patients with preexisting inflammatory arthritis commonly flare on ICIs but most of these flares can be managed with corticosteroids.