LEAP ROUNDS

Johns Hopkins University
School of Medicine
Division of Rheumatology
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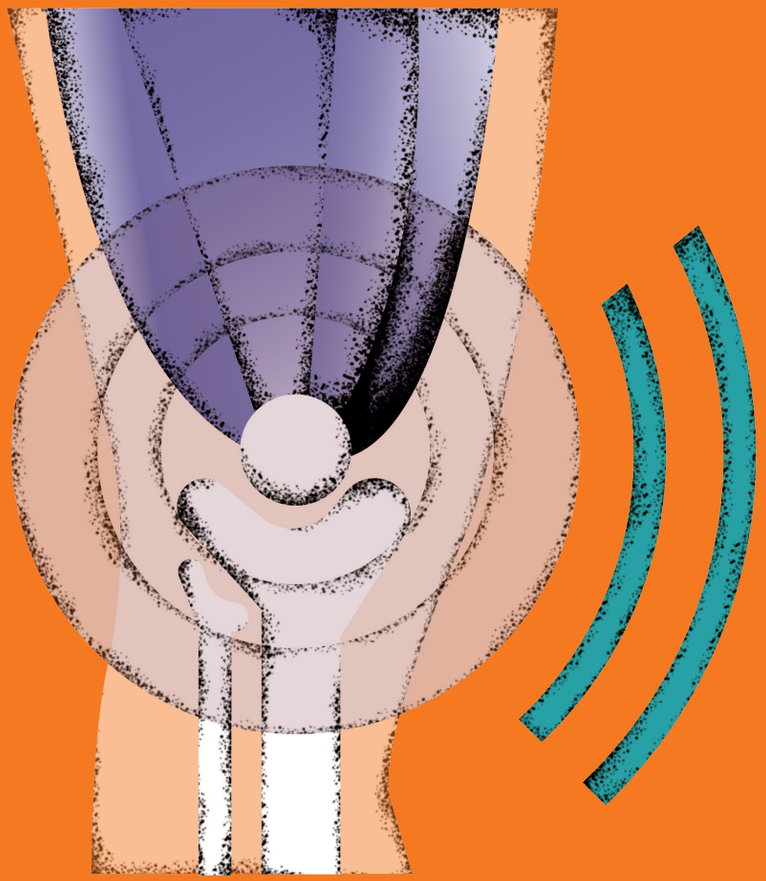
Immune Checkpoint Inhibitors and Inflammatory Arthritis

LAURA C. CAPPELLI, M.D., M.H.S.

ICIs Are Here to Stay, and So are irAEs

ICI-INDUCED INFLAMMATORY ARTHRITIS



INTERVIEW: LAURA C. CAPPELLI, M.D., M.H.S.

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many cancers, enabling long-term remission and potentially curative responses. But there's a downside: these drugs also can result in inflammatory syndromes known as *immune-related adverse events (irAEs)*. Of rheumatic irAEs, the most common is ICI-induced inflammatory arthritis (ICI-IA). Our program has been investigating and treating ICI-IA and other rheumatic irAEs since 2015.

ICIs Are Here to Stay, and So are irAEs

UP TO 7%

of patients treated with ICIs develop symptoms of inflammatory arthritis

There are now eight FDA-approved ICIs:

- ipilimumab
- nivolumab
- pembrolizumab
- atezolizumab
- avelumab
- durvalumab
- cemiplimab
- relatlimab

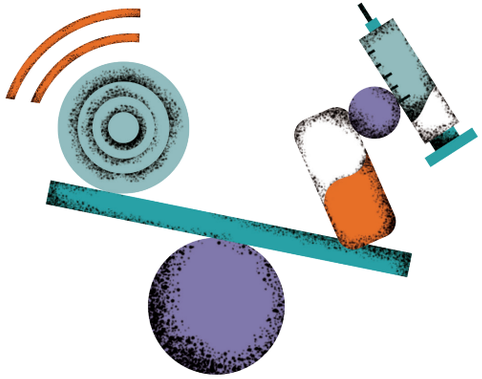
A 2018 study estimated that 44 percent of people in the U.S. with metastatic cancer were eligible for treatment with ICIs. As more novel ICI therapies are developed, the number of eligible patients – including high-risk patients being treated with adjuvant immunotherapy – will surely increase.

How do they work? ICIs use antibodies that target "checkpoints" (molecules that inhibit the activity of T cells) to boost the body's antitumor immune response. They fall into two basic categories: drugs that target the programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1), and drugs that focus on the cytotoxic T lymphocyte antigen-4 (CTLA-4). ICIs may be given along with chemotherapies or targeted agents, or in combination with each other (the only FDA-approved combination so far is nivolumab plus ipilimumab).

Recently, I was part of a panel that developed the Society for Immunotherapy of Cancer's clinical practice guidelines on irAEs. In a systematic review, we found that irAEs developed in 74% of patients treated with anti-PD-L1 inhibitors; in 89% of patients treated with anti-CTLA-4 inhibitors; and in 90% of patients treated with combination ICIs. irAEs are not uniquely the domain of the rheumatologist, because they can affect many organ systems, but rheumatologists are receiving more and more consults for irAEs including ICI-IA, polymyalgia rheumatica, myositis, and sicca syndrome. In another systematic review of ICI-associated events, between 1% and 7% of clinical trial participants developed arthritis. Many more patients – up to 40% in clinical trials – experience arthralgias. Although the vast majority of irAEs resolve by withholding treatment and institution of glucocorticoid therapy, ICI-IA does persist in a subset of patients.

A Delicate Balance

For ICI-IA, there is no set time limit: it can develop after the first infusion, during immunotherapy, or after the patient has finished ICI treatment. Treating ICI-IA requires a delicate balance: we want to decrease the off-target inflammation, but not harm the antitumor immune response and make the cancer worse! And ultimately, our shared decision-making (rheumatology and oncology working together) depends not only on the clinical presentation and severity of symptoms, but on the patient's goals.



We want to decrease the off-target inflammation, but not harm the antitumor immune response and make the cancer worse!

For example, highly motivated patients are willing to tolerate pain and limited mobility from ICI-IA just to stay on the medication.

At the Johns Hopkins Arthritis Center, we see multiple phenotypes of ICI-associated arthritis, including small joint-predominant polyarthritis similar to rheumatoid arthritis; large joint oligoarthritis frequently involving the lower extremities; symptoms that look like psoriatic arthritis; and rarely, symptoms of a reactive arthritis. In addition, patients may be experiencing arthralgia, joint stiffness and swelling that can affect their ability to perform their activities of daily living (ADL). On physical examination, we may also detect symmetrical synovitis with pitting edema; and musculoskeletal ultrasound highlights tendon involvement, with tenosynovitis and/or enthesitis. Most patients are seronegative for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Symptoms vary, as well, due to the type of ICI: Patients who are undergoing anti-PD1 monotherapy are more likely to present with small joint polyarthritis. Patients treated with anti-CTLA-4 therapy alone or in combination are more likely to develop knee arthritis.

We see Doppler-positive synovitis on ultrasound, joint effusions and synovitis on MRI, as well as erosions in severe cases.

Treatment Strategies

Close collaboration with the treating oncologist is essential.

At Johns Hopkins, we have an immune-related toxicity (IR-tox) team and a virtual tool that allows oncologists to connect with other providers to triage clinical questions. Treatment-related side

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Associate Professor of Medicine and Oncology at the Johns Hopkins University School of Medicine

Since 2015, she has been a thought leader in the clinical care of patients with inflammatory arthritis. She serves on national and international committees to develop treatment guidelines, diagnostic criteria, and research methods informing the approach to irAEs.

Dr. Cappelli's research program focuses on the rheumatologic adverse effects of cancer immunotherapy, including inflammatory arthritis, immune-mediated dry mouth and dry eyes, myositis, and vasculitis. She is investigating the clinical characteristics, epidemiology, impact on patients, and the biologic mechanisms of these drugs, in collaboration with oncologists and laboratory investigators in rheumatology and oncology.

effects are graded on a scale of 1 to 5, with most ICI-IA patients experiencing grade 1 or 2 severity:

- Grade 1: mild pain with erythema, inflammation, or joint swelling.
- Grade 2: moderate pain and limiting instrumental ADLs.
- Grades 3-5: Severe pain resulting in irreversible joint damage and limiting self-care ADLs.

Initial treatment for mild disease should be NSAIDs, followed by glucocorticoids.

Patients with limited large joint involvement may also benefit from intra-articular glucocorticoids. In case series of inflammatory arthritis, the overwhelming majority of patients are initially treated with glucocorticoids – most likely, because they developed symptoms severe enough to be referred to a rheumatologist. In our center's experience, for patients with moderate symptoms who have impairments in instrumental ADLs, prednisone 10-20 mg daily is a reasonable starting dose of steroids. Patients with more severe arthritis and functional limitation may begin with doses of 40-60 mg daily, and then taper. Patients with preexisting inflammatory arthritis (such as rheumatoid arthritis) tend to flare on ICI therapy, but can usually be managed with corticosteroids, and this should not be a contraindication to potentially lifesaving cancer treatment.

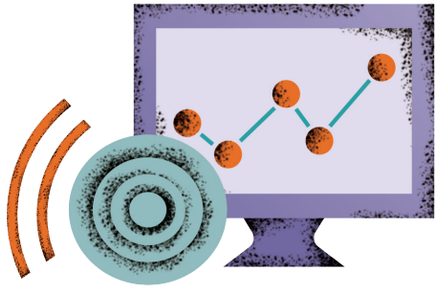
DMARDs:

For patients at risk of adverse effects from steroids, or patients unable to taper below 10 mg of prednisone daily, we suggest beginning a conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs), such as methotrexade, sulfasalazine, leflunomide, or hydroxychloroquine.

What about biologics? Patients who have been treated with glucocorticoids and csDMARDs who have refractory severe arthritis should be escalated to biologic therapy to prevent long-term joint damage and to regain functional status. Biologics also may be beneficial as a steroid-sparing agent in patients who need a faster time to arthritis improvement. For example: a patient in whom ICI therapy has temporarily been stopped because of toxicity; or, a patient with advancing cancer and a limited life span who wishes to achieve functional improvement to enjoy activities. In our experience at the Johns Hopkins Arthritis Center, patients usually report improvement after two or three doses of a subcutaneous TNF inhibitor. In contrast, response to csDMARDs tends to be slower.

Does Immunosuppression Affect the Cancer?

Can medication that *restrains* the immune system hamper the effectiveness of ICIs – drugs designed to *strengthen* the immune system? Yes and no. Short-term glucocorticoid exposure has not been shown to block the efficacy of ICIs in melanoma and other tumors. Nor has short-term TNF inhibition with 1-2 doses of infliximab been shown to affect the response to ipilimumab in melanoma. However, patients who received high-dose corticosteroids for hypophysitis had a worsened overall survival than those who only received adrenal replacement-dosed corticosteroids. And patients with non-small-cell lung cancer receiving prednisone 10 mg or higher had less response to anti-PD-1 and anti-PD-L1 agents.



Patients receiving combination immunotherapy should be given more frequent and prolonged monitoring.

What if Arthritis Persists?

For many patients, ICI-IA symptoms improve when the ICI is stopped. But a significant percentage of patients experience persistent arthritis. Of 126 patients in a recent study at our center, 114 had follow up with rheumatology at least 6 months after ICI cessation and 89 of those patients (78%) had persistent symptoms. Patients with persistent arthritis were more likely to have been treated with combination ICI therapy and have experienced two or more irAEs, and also to have had longer duration of ICI therapy. These results suggest that patients receiving combination immunotherapy should be given more frequent and prolonged monitoring. Of note: Numerous studies across various cancers have linked the development of an irAE with durable tumor response!

FURTHER READING

Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis.
Ann Rheum Dis.
2023, PMID:37019614

Spectrum and impact of checkpoint inhibitor-induced irAEs.
Nat Rev Rheumatol
2021, PMID:33235330

Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation.
Ann Rheum Dis.
2020, PMID:31540935

A Multidisciplinary Toxicity Team for Cancer Immunotherapy-Related Adverse Events.
J Natl Compr Canc Netw.
2019, PMID:31200355

Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab.
Ann Rheum Dis.
2017, PMID:27307501

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Physicians, nurse practitioners, pharmacists, oncologists, rheumatologists and other specialists on the Johns Hopkins immune-related toxicity (IR-tox) team, a group to triage clinical questions related to ICI-irAEs

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Hours or less: response time for IR-tox team referrals at Johns Hopkins

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