Arthritis Associated with Immune Checkpoint Inhibitors

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18.1 Introduction

Cancer treatment has been transformed with the development and approval of immune checkpoint inhibitors (ICI). Several ICIs have been approved for the treatment of cancer, providing remarkable survival benefits in both metastatic and adjuvant settings. Immune checkpoint inhibitors are monoclonal antibodies that target the regulatory immune checkpoints which inhibit T cell activation [1]. Thus, ICIs take the brakes off of the immune system enhancing the host's antitumor immune response. The approved ICIs are: (1) ipilimumab, and tremelimumab, which are antibodies against cytotoxic T lymphocyte-associated protein 4 (CTLA-4); (2) nivolumab, pembrolizumab, cemiplimab-rwlc, dostarlimab-gxly, and camrelizumab, which are antibodies against programmed death receptor-1 (PD-1); and (3) atezolizumab, durvalumab, and avelumab, which are antibodies against programmed death-ligand 1 (PD-L1). The use of combination therapy including 2 ICI with

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different mechanisms of action is becoming more common to address tumor resistance to treatment with a single agent.

Though effective in eliciting antitumor responses, ICIs often result in severe and occasionally fatal off-target inflammatory and autoimmune effects owing to unpredictable immune system activation against host organs [2]. While many of these immune-related adverse events (irAEs) are transient and resolve rapidly with immunosuppressive therapies and ICI discontinuation, some, especially, endocrinopathies, neurologic, and rheumatologic syndromes can have long-lasting effects and sequelae, significantly impacting patients' function and activities of daily living (ADL).

18.2 Epidemiology

Arthralgia can occur in up to approximately 40% of patients receiving ICI. Definite arthritis with synovitis is less frequent and has been reported in up to 9% of patients treated with ICI. However, the true incidence and severity of arthritis-irAE are still undetermined as most studies are retrospective case series [3]. Arthritis-irAE seems to be underreported in oncology trials that use the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE version 5.0 defines arthritis as grade II if it limits instrumental ADL, which from a rheumatology perspective is considered sufficient for treatment as musculoskeletal functional limitations severely affect the quality of life. However, many trials report primarily irAE grades III–V, and arthritis may have been initially underreported. Prospective longitudinal studies including denominators with all patients treated with ICI are necessary to accurately estimate the true incidence rate, severity, and outcome of arthritis-irAE.

18.3 Risk Factors

Arthritis-irAE occurs more frequently in patients receiving combination ICI therapy. A higher proportion of irAEs, in general, have been reported in Caucasians compared to African Americans; however, no racial association with arthritis-irAE was identified [4]. Although the female gender was found in one study to be an independent risk factor for irAE, it does not seem to be a risk factor for developing arthritis-irAE. Age has varied widely at presentation and does not appear to be independently associated with developing arthritis-irAE. Of note, body mass index $\geq$25 kg/m^2 was recently identified as a risk factor for irAE, including arthritis and other rheumatologic irAEs, in patients receiving anti-CTLA-4 or anti-PD-1/PD-L1 monotherapies, or ICI combination therapies [5]. As for cancer types, rheumatologic irAEs and arthritis-irAE may occur more frequently in patients with melanoma and genitourinary cancer receiving ICI [4]. Treatment with ICI combination therapy, glucocorticoid use within 1 year before ICI initiation, and history of preexisting autoimmune diseases are also associated with rheumatologic irAEs and

arthritis-irAE [4]. Notably, patients with preexisting inflammatory arthritis (rheumatoid, psoriatic, and spondyloarthritis) can experience arthritis flares upon ICI initiation, and this risk is higher among patients with active symptoms and in those who discontinued immunosuppressant therapy at ICI initiation. Moreover, the presence of autoantibodies including antinuclear antibodies (ANA), rheumatoid factor (RF), antithyroglobulin, and antithyroid peroxidase before ICI initiation have been identified as risk factors for developing irAEs, in general, although these results were not specific to rheumatologic irAEs or arthritis-irAE [6]. Some patients with arthritis-irAE were found to have preexisting anti-citric citrullinated peptide (anti-CCP) antibodies, suggesting that a pre-RA status can manifest clinically after ICI initiation. So far, no new autoantibodies have been identified in association with de novo arthritis-irAE.

18.4 Pathogenesis

Our understanding of the pathogenic mechanisms of irAEs, including arthritis-irAE, is still limited. Several mechanisms have been proposed [7]: (1) breach of self-tolerance and enhanced preexisting autoimmunity result from generalized immune activation induced by ICIs. In arthritis-irAE, immunoprofiling of the synovial fluid showed expanded $CD38^{hi}$ CD8 T cells and Th17 cells; (2) release of cytokines and chemokines from immune cells causing damage in tissues with an anatomic predisposition. Indeed, circulating cytokines such as the colony-stimulating factors (G-CSF and GM-CSF), chemokines (fractalkine), growth factors (FGF-2), interferons (IFNα2 and IFNγ), and interleukins (IL12p70, IL1α, IL1β, IL1RA, IL2, IL6, IL13, and IL-17) have been linked to irAEs development [6]. In arthritis-irAE, the successful use of antitumor necrosis factor (anti-TNF) and anti-IL-6 receptor (anti-IL-6R) antibodies for arthritis management suggest a role of these cytokines in pathogenesis [8, 9]; (3) cross-antigen reactivity against tumor-specific antigens and self-antigens released from healthy tissues located within and around the tumor milieu; (4) off-target effect of ICI therapy leading to damage in nonhematopoietic cells that express the target ligand; (5) genetic predisposition must play a role in irAEs susceptibility. Germline genetic features identified through small pilot studies suggested shared biological pathways between irAEs development and autoimmune diseases [6]. Of note, carriers with interferon-gamma (IFNG)—1616T > C single nucleotide polymorphism homozygous variant were found to have an increased risk for rheumatologic irAEs, and the presence of human leukocyte antigen (HLA) DRB1 shared epitope alleles (a known risk factor for rheumatoid arthritis) was found to be higher in patients with arthritis-irAE compared with healthy controls; and (6) apart from the usual factors, gut microbiota, primarily Bacteroides intestinalis were associated with irAEs development in ICI combination therapy-treated patients [6].

18.5 Clinical Features

Arthritis-irAE can present anytime after initiation of ICI therapy; immediately after receiving the first dose or as a late adverse event (AE) occurring 44 months post-treatment, and it may persist even after ICI discontinuation. Some patients may initially present with arthralgia, with or without joint stiffness, but develop overt synovitis over time. Most patients developing arthritis-irAE have an undifferentiated clinical presentation that does not always fulfill diagnostic criteria for primary autoimmune inflammatory arthritis. We describe below the most common patterns (Table 18.1):

Undifferentiated inflammatory arthritis: Patients may present with oligoarthritis or polyarthritis of large joints such as knees, ankles, or wrists, which can be symmetric or asymmetric in distribution [10]. Sometimes patients present with monoarthritis. These patients are negative for RF and anti-CCP, although some may be ANA positive. They generally have normal radiographs at presentation; however, they can have persistent inflammation resulting in erosive disease [11, 12].

Table 18.1 Clinical phenotypes of immune checkpoint inhibitor-induced inflammatory arthritis

Clinical pattern	Presentation
Undifferentiated inflammatory arthritis	– Oligoarthritis or polyarthritis of large joints (symmetric or asymmetric in distribution) – Monoarthritis has been reported – Negative RF and/or anti-CCP antibodies – ANA may be positive
Rheumatoid arthritis-like	– Symmetrical polyarthritis involving small joints of the hands and wrists – Positive RF and/or anti-CCP antibodies
Seronegative spondyloarthropathy-like	– Oligo/polyarthritis and axial disease or enthesopathy – Psoriatic arthritis with/without skin changes – Reactive arthritis – Negative HLA-B27
Polymyalgia rheumatica-like	– Morning stiffness and pain of shoulders and hips – Elevated ESR and CRP – Negative RF and anti-CCP antibodies – Concomitant arthritis has been reported – Concomitant giant cell arteritis has been reported
Remitting seronegative symmetrical synovitis with pitting edema	– ESR and CRP may be elevated – Negative autoantibodies
Tenosynovitis	– ANA may be positive

RF Rheumatoid factor, *anti-CCP* Anti-citric citrullinated peptide, *ANA* Antinuclear antibodies, *HLA-B27* Human Leukocyte Antigen B-27, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein

Rheumatoid arthritis (RA)-like: Patients may present with symmetrical polyarthritis predominantly involving small joints of the hands and wrists, along with positive RF and/or anti-CCP antibodies in their sera, fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) diagnostic criteria for rheumatoid arthritis (RA) [10]. While not commonly reported, this pattern is potentially erosive and may lead to permanent joint damage.

Seronegative spondyloarthropathy (SPA)-like: In addition to oligo/polyarthritis, some patients present with axial disease (inflammatory back pain or cervical pain) and enthesopathy (pain/tenderness in connective tissues between bones and tendons or ligaments such as the heel or iliac crest) [12]. The facet, costovertebral, and sacroiliac joints are involved [12, 13], but unlike primary spondyloarthritis, the few reported patients tested negative for Human Leukocyte Antigen (HLA)-B27 alleles. Moreover, ***psoriatic arthritis with and without skin changes*** also presents following ICI initiation; all reported patients were seronegative and none had a prior history of psoriasis [10]. The triad of ***reactive arthritis*** (arthritis, conjunctivitis, and sterile urethritis) has been observed in some patients, especially after receiving ICI combination therapy [10, 12].

Polymyalgia rheumatica (PMR)-like: Some patients present with morning stiffness and pain of both shoulders and hips, with elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and negative RF and anti-CCP antibodies, fulfilling the 2012 EULAR/ACR classification criteria for polymyalgia rheumatica (PMR) [14]. In these patients, joint swelling is not typical, but some develop effusions in shoulders/hips, subdeltoid bursitis, or biceps tenosynovitis, which can be seen by ultrasound or MRI.

PMR/arthritis overlap: Some patients have atypical PMR features with inflammatory arthritis involving other joints most commonly the knees, followed by the small joints of the hands and elbows. A few patients have been reported presenting with normal inflammatory markers. Patients with PMR have normal muscle strength and creatine kinase (CK) levels within normal limits. Unlike primary PMR, patients with PMR-irAE may require higher doses of glucocorticoids, exceeding 20 mg daily of prednisone.

Concomitant ***giant cell arteritis*** (GCA) has been occasionally reported, with patients presenting with jaw claudication, temporal headache, scalp tenderness, and vision loss.

Remitting seronegative symmetrical synovitis with pitting edema has been reported following ICI therapy, while all reported patients had elevated ESR and CRP and were negative for autoantibodies [10, 15].

Tenosynovitis: Some patients develop tenosynovitis in the hands, forearms, shoulders, and/or knees. Tenosynovitis may occur either alone or associated with arthritis. A few patients were found to be ANA positive [16].

Further studies are required to understand why patients present with such different clinical patterns. For some presentations such as RA-like, or psoriatic arthritis, it is possible that patients may have a preexisting subclinical disease or predisposing genotypes, and that therapy with ICI triggers the subsequent clinical disease. Some patients who developed RA-like arthritis were found to have RF and/or anti-CCP

antibodies in serum before they received ICI [6]. Some patients with cutaneous psoriasis also developed psoriatic arthritis after ICI treatment. One study has reported variations in clinical presentation and outcomes in patients receiving anti-PD1 alone compared to those receiving ICI combination [12]. Patients receiving single-agent anti-PD1 were more likely to develop arthritis-irAE as the only toxicity, presenting with small joints arthritis. On the other hand, those who received ICI combination were more likely to develop multiple other irAEs and to present with knee arthritis [12]. Persistence of arthritis-irAE after ICI discontinuation was reported in more than 50% of the patients in this cohort [17] and was associated with having received ICI combination, and with a longer duration of ICI treatment.

18.6 Diagnosis

The ACR generally recommends five measures for RA disease activity including (1) clinical disease activity index (CDAI); (2) simple disease activity index (SDAI); (3) disease activity score-28-ESR (DAS28 ESR); (4) disease activity score-28-CRP (DAS-28 CRP), and routine assessment of patient index data 3 (RAPID 3) and three measures for RA functional assessment including (1) health assessment questionnaire-II (HAQ-II); (2) patient activity scale II (PAS II); and patient-reported outcomes measurement information system short form—physical function 10a (PROMIS PF10a) for use in clinical practice. While few of these measures have been utilized for evaluating patients with arthritis-irAE, they still need to be validated in this setting.

Laboratory testing should include: (1) ESR and CRP, which are typically elevated in patients with active inflammatory symptoms although not seen in all patients with arthritis-irAE; (2) ANA, RF, and anti-CCP, most patients predominantly those with undifferentiated arthritis are typically negative; (3) HLA-B27 primarily in patients presented with seronegative spondyloarthropathy-like arthritis; (4) Muscle enzymes in patients presenting with PMR-like arthritis, though are typically normal; (5) Joint aspiration and synovial fluid analysis, which typically reveals inflammation with neutrophilic predominance; and (6) hepatitis B and C, human immunodeficiency virus (HIV), and tuberculosis primarily if patients will require immunosuppressive therapies as this may result in reactivation of latent infection. Of note, several biomarkers (blood-based, immunogenetic, and microbial) were suggested as predictors for irAEs development, including endocrine toxicities, colitis, dermatitis, and pneumonitis [6]. However, predictive biomarkers for arthritis-irAE have not been suggested yet. Future studies with a prospective standardized collection of biospecimens (blood and synovial fluid) are important to identify predictive biomarkers for arthritis-irAE.

Imaging can be employed to confirm diagnosis early on and to exclude other possible causes of arthritis. Plain radiography of the affected joints can detect joint erosions and joint space narrowing. Whereas ultrasound and magnetic resonance (MRI) images can detect synovitis, inflammatory signals, tendinitis, enthesopathy, and erosions [11]. Importantly, in patients presenting with PMR-like along with features suggestive of GCA, urgent ophthalmological exam and temporal artery

biopsy should be considered due to the known risk of permanent blindness with this type of vasculitis. Also, MRI, electromyography, or muscle biopsy may be considered to exclude muscle inflammation or myopathy in case of diagnostic uncertainty. Close monitoring is required for patients with arthritis-irAE with periodic clinical evaluations including joint examination and serial testing of inflammatory markers (ESR and/or CRP) every 4–6 weeks to monitor the therapeutic response until symptoms improve. Imaging should also be repeated to follow up for structural damage.

18.7 Differential Diagnosis

At presentation, clinicians typically confirm that symptoms started after initiation of ICI and exclude other conditions that may cause similar symptoms including preexisting autoimmune disease, osteoarthritis, or crystal arthritis as few patients have been reported with worsening or recurrent symptoms following ICI initiation. Paraneoplastic arthritis should also be excluded especially if symptoms started around the time of cancer diagnosis. Additionally, metastatic disease within the adjacent bone or joint structures, and septic arthritis should be excluded primarily in patients with monoarthritis.

18.8 Management

The guidelines for the management of irAEs have been published by several key oncology and rheumatology societies, based on the severity of presentation as per CTCAE grades [8, 9]. For arthritis-irAE, a prompt rheumatology consult is recommended if there is joint pain for more than 4 weeks, joint swelling, arthritis ≥ grade 2, or unable to taper corticosteroids to <10 mg/day within 4 weeks, and to identify signs of joint damage early on. Afterward, an assessment should be made for the need for arthrocentesis/intra-articular corticosteroid injection, and initiation/optimal dosing of disease-modifying anti-rheumatic drugs (DMARDs). The decision to initiate ICI therapy in patients with preexisting inflammatory arthritis requires a rheumatology-oncology multidisciplinary approach to carefully weigh the benefit/risk ratio while considering the severity of the underlying autoimmune disease, the prognosis of cancer, alternative therapies, and patients' preferences. For these patients, it is important to keep their baseline immunosuppressive regimen at the lowest efficient dose before ICI initiation as these patients are at high risk of arthritis flare after therapy initiation. Generally, the existing guidelines define three treatment escalations for arthritis-irAE, which are summarized in Table 18.2 [8, 9].

Mild arthritis-irAE (grade 1 per CTCAE): Patients with mild arthritis with no functional impact on their ADL are managed with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) if there is no contraindication, and/or intra-articular corticosteroid injection. Continuation of ICI therapy is recommended. However, if arthritis does not improve within 4 weeks, treatment should be escalated to the next step.

Table 18.2 Current guidelines for the management of checkpoint inhibitor-induced inflammatory arthritis

Clinical pattern	Presentation
Mild arthritis-irAE (grade 1 per CTCAE)	– Acetaminophen or NSAIDs if no contraindication – Intra-articular corticosteroid injection – Continue ICI therapy – Escalate treatment to next step if no improvement of arthritis within 4 weeks
Moderate arthritis-irAE (grade 2 per CTCAE)	– Oral prednisone 10–20 mg/day or equivalent – Intra-articular corticosteroid injection – Consider holding ICI therapy – Taper corticosteroid within 4–6 weeks if arthritis improved – Escalate treatment to next step and initiate DMARDs if no improvement of arthritis within 4 weeks or if unable to taper corticosteroids to below 10 mg/day within 6–8 weeks
Severe arthritis-irAE (grade 3 and 4 per CTCAE)	– Oral prednisone 0.5–1 mg/kg/day – Taper corticosteroid within 4–6 weeks if arthritis improved – Escalate treatment to next step and initiate DMARDs if no improvement or worsening of arthritis within 2 weeks Cs-DMARDs (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide alone or in combination) b-DMARDs (anti-TNF or anti-IL-6R)

CTCAE Common Terminology Criteria for Adverse Events, *NSAIDs* Non-steroidal anti-inflammatory drugs, *ICI* immune checkpoint inhibitor, *DMARDs* Disease-modifying anti-rheumatic drugs, *cs-DMARDs* Conventional synthetic DMARDs, *b-DMARDs* biological DMARDs, *anti-TNF* Antitumor necrosis factor, *anti-IL-6R* Anti-IL-6 receptor

Moderate arthritis-irAE (grade 2 per CTCAE): Patients with moderate arthritis with functionally impacted ADL, but not interfering with self-care are managed with 10–20 mg/day of oral prednisone or equivalent for 4 weeks, and intra-articular corticosteroid injection if ≤2 large joints are involved. ICI therapy should be placed on temporary hold. If arthritis improves, oral prednisone should be tapered slowly over 4–6 weeks, and ICI therapy should be resumed when prednisone is ≤10 mg/day. However, if arthritis does not improve within 4 weeks, or if unable to taper prednisone to ≤10 mg/day after 6–8 weeks, treatment should be escalated to the next step and initiation of DMARDs is recommended.

Severe arthritis-irAE (grade 3 and 4 per CTCAE): Patients with severe arthritis impacting self-care and ADL are managed with 0.5–1 mg/kg/day of oral prednisone or equivalent. ICI therapy should be placed on temporary hold. If arthritis improves, oral prednisone should be tapered slowly over 4–6 weeks, and treatment with ICI should be resumed when prednisone is ≤10 mg/day. However, if arthritis does not improve within 2 weeks or if worsening of symptoms is noted, initiation of conventional synthetic DMARDs (cs-DMARDs) is recommended; methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide (alone or in combination) are the most common at doses used to treat RA. In case of severe or refractory arthritis, the use of certain biological DMARDs (b-DMARDs) such as anti-TNF or anti-IL-6R antibodies is recommended. One should keep in mind that persistent inflammation, as well as treatment with corticosteroids (prednisone of ≥2.5 mg/day or equivalent for ≥3 months), increase the risk of osteoporosis, and therefore patients with arthritis-irAE should be encouraged to maintain a healthy lifestyle with adequate nutrition

and weight-bearing exercises and may require pharmacological therapy [18]. While on DMARDs, these patients also need close monitoring of neutrophil and platelet counts, serum lipids, liver transaminases, and serum creatinine. If arthritis improves to grade 1, ICI therapy should be resumed but should be discontinued permanently if there is no improvement after 4–6 weeks of treatment.

Finally, it is worth mentioning that the occurrence of irAEs has been suggested as a surrogate for effective antitumor immune response; patients with any grade irAEs were found to have higher objective response rate, disease control rate, and overall survival, and those with grade 2 or higher irAEs or multiple irAEs had better progression-free survival and overall survival [19]. Similarly, patients who develop rheumatic and musculoskeletal irAEs per se were found to have better tumor response [20]. Therefore, future studies should focus on investigating how we can effectively manage irAEs without hindering the antitumor immune response to ICI therapy. While published guidelines endorse corticosteroids as first-line therapy for irAEs, targeted therapies could be safer and preferable to corticosteroids especially for arthritis-irAE, which may likely require prolonged therapy. Studies from melanoma and non-small cell lung cancer patients treated with ICIs have shown that the use of prednisone ≥10 mg/day led to detrimental cancer outcomes and worsen survival [21, 22]. Also, the timing of treatment initiation was found to affect the response to ICI therapy; patients treated with corticosteroids within the first 2 months after ICI initiation had shorter progression-free survival and overall survival as compared to those who received corticosteroids later [23]. With regard to corticosteroid-sparing agents, one study showed that the use of cs-DMARDs or b-DMARDs for arthritis-irAE did not impact the tumor response to ICI [17]. However, another study showed that the use of hydroxychloroquine led to decreasing the efficacy of anti-PD-1 agents [24]. Players in the autoimmune pathways can be targeted, such as TNF-alpha, but, given its role in antitumor immunity, concerns remain regarding the safety of prolonged anti-TNF therapy and its impact on survival [25]. On the other hand, anti-IL-6R antibody shows promising results for irAE management; a recent systematic review of the literature provided data on 91 patients, where the use of tocilizumab resulted in clinical benefit and none of them were reported with tumor progression [26]. Another study that combined translational, preclinical, and clinical analyses, identified that targeting IL-6 could be an effective approach for irAE management while maintaining and possibly boosting tumor immunity [27]. However, anti-IL-6R antibody might not be suitable for patients who also had colitis-irAE or preexisting inflammatory bowel disease due to the potential risk of intestinal perforation, although isolated case reports have not shown complications in these patients [28, 29]. To date, there is only one published case reporting the use of tofacitinib; JAK inhibitor, for treatment of arthritis-irAE in a patient with metastatic lung adenocarcinoma who achieved remission of arthritis and cancer [30]. However, the FDA has recently announced a black box warning on tofacitinib use due to concerns about the increasing risk of serious cardiovascular adverse events, thrombosis, cancer, and death. To our knowledge, 15 clinical trials are currently investigating the use of therapies for prevention and management of irAEs in patients receiving ICI therapy (Table 18.3).

Table 18.3 Current clinical trials investigating targeted therapies for the management of immune-related adverse events

Clinical trials	Trial ID	Status
Tocilizumab, ipilimumab, and nivolumab for the treatment of advanced melanoma, non-small cell lung cancer, or urothelial carcinoma	NCT04940299	Recruiting
Study of rituximab or tocilizumab for patients with steroid-dependent immune-related adverse events (irAEs)	NCT04375228	Recruiting
Checkpoint inhibitor-induced colitis and arthritis—Immunomodulation with IL-6 blockade and exploration of disease mechanisms (COLAR)	NCT03601611	Completed
A phase II study of the Interleukin-6 receptor inhibitor tocilizumab in combination with Ipilimumab and Nivolumab in patients with Unresectable stage III or stage IV melanoma	NCT03999749	Recruiting
TNF-inhibitor as immune checkpoint inhibitor for advanced MELanoma	NCT03293784	Active, not recruiting
Infliximab or Vedolizumab in treating immune checkpoint inhibitor-related colitis in patients with genitourinary cancer or melanoma	NCT04407247	Recruiting
Role of gut microbiome and fecal transplant on medication-induced GI complications in patients with cancer	NCT03819296	Recruiting
Ipilimumab, Nivolumab, tocilizumab, and radiation in pretreated patients with advanced pancreatic cancer	NCT04258150	Terminated (primary endpoint was not met)
Atezolizumab with or without tocilizumab in treating men with prostate cancer before radical prostatectomy	NCT03821246	Recruiting
A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with advanced liver cancers (Morpheus-liver)	NCT04524871	Recruiting
A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with metastatic or inoperable locally advanced triple-negative breast cancer	NCT03424005	Recruiting
Study evaluating the efficacy and safety of multiple immunotherapy-based treatments and combinations in patients with urothelial carcinoma (MORPHEUS-UC)	NCT03869190	Recruiting
Tofacitinib for the Treatment of Refractory Immune-related Colitis From Checkpoint Inhibitor Therapy- TRICK Study	NCT04768504	Recruiting
Treatment Efficacy of Corticosteroids, Mycophenolate Mofetil and Tacrolimus in Patients With Immune Related Hepatitis (IHEP)	NCT04810156	Not yet recruiting
Fecal Microbiota Transplantation in Treating Immune-Checkpoint Inhibitor Induced-Diarrhea or Colitis in Genitourinary Cancer Patients	NCT04038619	Recruiting

18.9 Conclusion

Immune checkpoint inhibition has transformed cancer treatment. However, ICIs often result in off-target inflammatory and autoimmune effects. The chances of irAEs are higher in those with preexisting autoantibodies and rheumatic diseases.

Thus, the decision to initiate ICIs in such patients should be taken in consultation with a rheumatologist. Treatment of arthritis irAEs involves temporary withdrawal of the ICI and the administration of NSAIDs, glucocorticoids, and/or DMARDs depending upon the severity of the irAE. Rare cases may however require permanent discontinuation of ICI therapy.

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