TABLE 5. Musculoskeletal Toxicities

5.1. IA

Workup and evaluation

G1

Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion. Examination of the spine.

Consider plain X-ray or imaging to exclude metastases and evaluate joint damage (erosions) if appropriate.

Consider autoimmune blood panel including ANA, RF, anti-CCP, and inflammatory markers (ESR and CRP) if symptoms persist. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing.

G2:

Complete history and examination as above; laboratory tests as above.

Consider ultrasound ± MRI imaging of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, and suspicion for differential diagnoses such as metastatic lesions or septic arthritis). Consider arthrocentesis if septic arthritis or crystal-induced arthritis is suspected.

Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persist > 4 weeks.

G3-4:

As for grade 2.

Seek rheumatologist advice and review.

Test for viral hepatitis B, C, and latent or active TB test before DMARD treatment. Repeated screening labs annually in patients who require biologic treatment for > 1 year until treatment is completed.

Monitoring

Patients with IA should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptoms new since receiving ICPi.
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi. Initiate analgesia with acetaminophen and/or NSAIDs.
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Consider holding ICPi. Escalate analgesia and consider higher doses of NSAIDS as needed. If inadequately controlled, initiate prednisone 10-20 mg/d or equivalent. If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4 weeks treat as G3. If unable to lower corticosteroid dose to below 10 mg/d after 6-8 weeks, consider DMARD. Consider intra-articular steroid injections for large joints. Referral to rheumatology.
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; and limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to ≤ G1. Initiate oral prednisone 0.5-1 mg/kg. If failure of improvement after 2 weeks or worsening in meantime, consider synthetic or biologic DMARD. Synthetic: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine alone or in combination. Biologic: Consider anticytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL6 inhibition can cause intestinal perforation.[141] Although this is extremely rare, it should not be used in patients with concomitant immune-related colitis. Referral to rheumatology.

Additional considerations

Early recognition is critical to avoid erosive joint damage.

Corticosteroids can be used as part of initial therapy in IA, but because of likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs.

Oligoarthritis can be treated early on with intra-articular steroids, consider early referral.

5.2. Myositis

Workup and evaluation

Complete rheumatologic and neurologic history regarding differential diagnosis and rheumatologic and neurologic examination including muscle strength, and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms.

Blood testing to evaluate muscle inflammation, CK, and aldolase. Transaminases (AST and ALT) and LDH can also be elevated.

Troponin to evaluate myocardial involvement. Other cardiac testing such as ECG and echocardiogram or cardiac MRI (see CV section for further details).

Autoantibody testing to evaluate possible concomitant myasthenia gravis (anti-AChR and antistriational antibodies)

Inflammatory markers (ESR and CRP).

Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes such as myasthenia gravis is suspected.

Consider paraneoplastic autoantibody testing for myositis (eg, anti-TIF1γ, anti-NXP2, and other myositis autoantibodies as indicated), especially if patient had muscle-related manifestations before receiving ICPi

Urinalysis for rhabdomyolysis.

Monitoring

CK, ESR, CRP, and aldolase if CK has not been elevated.

G1: Complete examination and laboratory workup as above.

G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI imaging of affected joints. Early referral to a rheumatologist or neurologist.

G3-4: As for grade 2. Urgent referral to a rheumatologist or neurologist.

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