Monitoring and Management of Rheumatologic Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitor Therapy

By Dr. Shahin Jamal

Key principles of rheumatologic immune-related adverse events (irAEs)

- Rheumatologic irAEs include **arthralgia, myalgia, inflammatory arthritis, polymyalgia rheumatica (PMR)-like syndromes, and myositis**, often with negative autoimmune serologies
- The goal is **symptom control and function**; not necessarily remission, while preserving anticancer benefit
- Any immunosuppressive treatment (steroids, DMARDs, biologics) **may impact tumour control**; decisions are empirical and depend on cancer context (curative, adjuvant, palliative) and patient goals
- Emerging data show that delayed immunosuppression is associated with better outcomes
- There are no data on best practices for management
- Patients should be counselled on the risk of chronic ICI inflammatory arthritis

Best practices checklist

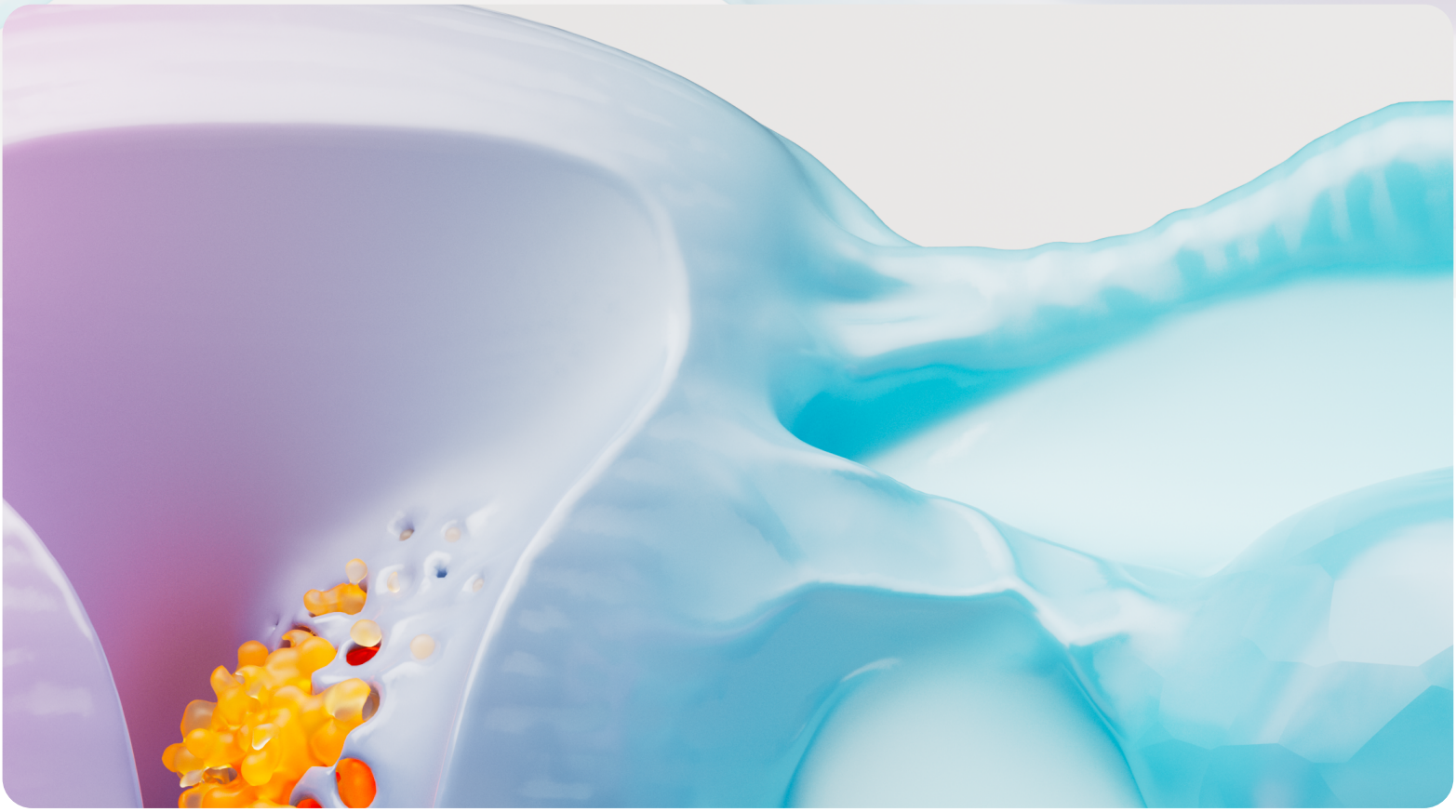
- Baseline assessment
  - **Brief musculoskeletal history** (pre-existing inflammatory arthritis, PMR, myositis, autoimmune disease)
  - Consider a **baseline CRP** (most helpful if low at baseline); repeat if new musculoskeletal symptoms develop
  - **Evaluate for "triple M"** (co-occurrence of myositis, myocarditis, myasthenia; mortality rate ~50%)
    - **Check creatine kinase; if elevated, be concerned about subclinical myocarditis (can be subclinical; only arrhythmia)**
    - **Hold IO, escalate workup (troponin, ECG ± echo) and consult rheumatology/cardiology with admission/ER for bulbar or respiratory involvement**
- At each visit, ask about:
  - New inflammatory joint pain or **morning stiffness**
  - Swelling, reduced range of motion, difficulty with **activities of daily living**
  - New **muscle weakness**, especially proximal or neck extensor weakness
  - Check **creatine kinase**
- Shared decision-making
  - Key treatment decisions (holding/continuing IO, starting DMARD/biologic) should be shared between oncology, rheumatology, and the patient, balancing cancer prognosis, irAE severity, alternatives, and patient preference

When to refer to rheumatology (early is better)

- Prolonged steroid treatment
- Joint swelling
- CTCAE grade 2 and above symptoms
- Symptoms persisting for more than 6 weeks or requiring prednisone 20 mg daily or equivalent that cannot be tapered to <10 mg/day within 4 weeks
- Suspected myositis, presenting with muscle weakness and elevated creatinine

ICI inflammatory arthritis

- Often **seronegative** (RA-like polyarthritis, oligoarthritis, monoarthritis) or **PMR-like** shoulder/hip girdle pain and stiffness; presentation is highly variable
- Chronic arthritis is common (80%) and may not remit when IO is stopped
- **Disease is often** severe and significantly impacts long-term quality of life
- Often requires higher doses of immunosuppression than idiopathic disease
- Onset is often 10–12 months after starting treatment; can occur after stopping treatment
- **Generally associated with better cancer outcomes**
- **Principles of immunosuppression for ICI-IA:**
  - Use the **lowest effective steroid dose for the shortest time**
    - Starting steroids later is better
    - Prednisone <10 mg/day is associated with better cancer outcomes; **>20 mg/day** is associated with worse outcomes
    - Conventional DMARDs (MTX, HCQ, SSZ, MMF) appear **relatively safer** than traditional biologics (e.g. TNFi, IL-6i, abatacept), which confer greater immunosuppression
- ICI can be held with similar tumor outcomes to remaining on ICI
- About **50% of patients with ICI-arthritis flare** when immunotherapy is restarted; most flares are manageable, and many patients can continue ICIs



CTCAE, Common Terminology Criteria for Adverse Events; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ECG, electrocardiogram; ER, emergency room; HCQ, hydroxychloroquine; ICI, immune checkpoint inhibitor; ICI-IA, immune checkpoint inhibitor inflammatory arthritis; IL, interleukin; IO, immuno-oncology drug; irAE, immune-related adverse events; MMF, mycophenolate mofetil; MTX, methotrexate; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SSZ, sulfasalazine; TNFi, tumour necrosis factor inhibitor.

1. Fontenot AP et al. *J Clin Invest*. 2003;112:776–784. 2. Janeway CA Jr et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York: Garland Science Publishing; 2005. 3. Jamal S et al. *J Rheumatol*. 2020;47:166–75. 4. Kostine M et al. *Ann Rheum Dis.* 2021 Jan;80(1):36–48. 5. Ladouceur A et al. ACR *Open Rheumatology*. Jan 2025. 6. Paul WE, ed. Fundamental Immunology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2003. 7. Soukup T et al. *J Multidiscip Health*. 2018 Jan 19;11:49–61. 8. Tawnie et al. *Ann Rheum Dis*. 2020. 9. Ye C et al. *J Rheumatol*. 2025;52(10).