

## **Immune Checkpoint Inhibitor Induced Inflammatory Arthritis**

Arthralgias are common in cancer patients treated with immunotherapy. A smaller percentage of patients develop inflammatory musculoskeletal conditions including inflammatory arthritis and a polymyalgia rheumatica-like syndrome. Considerations in the diagnosis and management of immune checkpoint inhibitor-associated inflammatory arthritis (ICI-IA) are discussed below.

### *How Does ICI-IA present?*

The most commonly reported pattern of ICI-IA is a symmetrical polyarticular inflammatory arthritis with small joint involvement. Clinically, this presentation of ICI-IA is similar to idiopathic rheumatoid arthritis however is typically seronegative (negative rheumatoid factor and cyclic citrullinated peptide antibodies). Periarticular involvement including tenosynovitis is common, with some patients presenting with diffuse swelling of the involved areas. Other presentations include a polymyalgia rheumatica-like syndrome with proximal shoulder and hip girdle pain and stiffness often associated with elevated inflammatory markers; psoriatic arthritis with skin, nail and joint involvement; oligoarticular or monoarticular inflammatory arthritis often involving large joints and reactive arthritis with sterile conjunctivitis and urethritis. Worsening osteoarthritis and a variety of non-inflammatory musculoskeletal conditions such as tendonitis, bursitis and adhesive capsulitis have also been described.

### *How is ICI-IA treated?*

Treatment recommendations for ICI-IA involves a stepwise approach based on disease severity. For mild disease pain control with acetaminophen and non-steroidal anti-inflammatory medications is suggested. For medium to large joints, amenable to injection, intra-articular steroid injections can be considered. For moderate disease, low dose prednisone 10-20 mg daily is suggested with doses up to 0.5 to 1 mg/kg required in the event of severe disease. Conventional synthetic disease modifying antirheumatic drugs (DMARDs) and biologic DMARDs may be required for disease control and steroid-sparing effects. The optimal timing of DMARD initiation remains largely unknown. In many cases ICI-IA is persistent, even after ICI discontinuation, and thus early initiation of DMARDs should be considered. In some cases early diagnosis and initiation of DMARDs may allow patients to avoid steroids completely. In those not responding to conventional DMARDs, biologic DMARDs can be considered with TNF-inhibitors and IL-6 inhibitors being the preferred agents.

### *Should immunotherapy be discontinued in the event of ICI-IA?*

The decision to hold or discontinue immunotherapy should be shared between the patient, rheumatologist and oncologist with important considerations being arthritis severity, tumour response to immunotherapy and planned duration of immunotherapy. Permanent discontinuation is rarely required however temporary discontinuation may be considered in the setting of moderate to severe arthritis.

### *Does treatment of ICI-IA negatively impact the anti-tumour response?*

Prolonged treatment with steroids, particularly at higher doses (>10 mg daily) can negatively impact the efficacy of immunotherapy. When symptom control is achieved steroids should be tapered to the lowest possible dose to control symptoms. If patients require prednisone at doses greater than 10 mg daily to control their symptoms a DMARD should be considered. Based on the data available at present conventional DMARDs used to treat ICI-IA are safe and do not attenuate the anti-tumour response. The commonly reported DMARDs used in ICI-IA are hydroxychloroquine and methotrexate. Similarly, TNF-inhibitors and IL-6 inhibitors appear safe. Loss of tumour response following treatment with an IL-17 inhibitor has been reported and thus this class of medication should be avoided.