ADLs = activities of daily living; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CR = creatinine; CRP = C-reactive protein; DDI = degenerative joint disease; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IA = immune-related adverse event; IAEs = immune-related adverse events;IQR = interquartile range; IP = irAE; IPILimumab = Ipilimumab; JAK = Janus kinase; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; po = by mouth; QOL = quality of life; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumor necrosis factor.

**Grading Toxicty**

**Arthralgia**

Definition: A disorder characterized by a sensation of marked discomfort in a joint

**Arthritis**

Definition: A disorder characterized by inflammation involving a joint

**Management**

**Overall Strategy:**
- Avoid or reduce chemotherapeutic agents
- Early intervention to maintain or improve physical function and impact on QOL; symptom control through the treatment of inflammation and pain is often achieved with NSAIDs, corticosteroids, and other adjunct therapies

**Grade 1 (Mild)**
- Mild pain with joint swelling
- Does the patient have moderate pain?
- Is gait affected?
- Does the patient have difficulty getting up or down stairs?
- Is extremely dry skin? Extremely red/dry eyes?
- Listen:
  - Is there morning stiffness lasting longer than 30 minutes?
  - Have symptoms worsened?
  - Are symptoms limiting ADLs?
  - Are symptoms increasing the patient’s risk for fall? Other safety issues?
  - Associated symptoms?
- History:
  - Ten days of low-grade fever
  - Report of extreme dry mouth, dry eyes?
  - Difficulty swallowing?

**Grade 2 (Moderate)**
- Moderate pain limiting instrumental ADL
- Low-dose corticosteroids* (0.5 mg/kg/day) to be used
- Intraarticular steroids to be used for significant limited, lasting for about 4–6 weeks, with possible resolution of symptoms within weeks to months of treatment
- Assess patient & family understanding of toxicity and rationale for treatment hold (if applicable)
- Identify barriers to adherence
- If symptoms do not improve in 4–6 weeks, escalate to next level of therapy

**Grade 3 (Severe)**
- Severe pain limiting self-care ADL
- Continue to encourage physical activity
- Risk of fall due to mobility issue
- Risk of exacerbation of disease
- Anticipatory guidance on proper administration
- Low-dose NSAIDs if cannot tolerate oral NSAIDs
- Anti B-cell agents (CD-20 blocking)
- Intraarticular steroids to be used for significant limited, lasting for about 4–6 weeks, with possible resolution of symptoms within weeks to months of treatment
- Assess patient & family understanding of toxicity, rationale for treatment hold (if applicable)
- Identify barriers to adherence
- If symptoms do not improve in 4–6 weeks, escalate to next level of therapy

**Grade 4 (Potentially Life-Threatening)**
- Pembrolizumab or nivolumab to be withheld if for first-occurrence Grade 3 event and permanently discontinued if:
  - Grade 3 event recurs
  - Pemetrexed
  - Pembrolizumab or nivolumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥12 weeks
  - Concur to encourage physical activity
  - Anticipatory guidance on proper administration
  - Assess patient & family understanding of recommendations and rationale
  - Identify barriers to adherence

**Grade 5 (Death)**
- Pembrolizumab or nivolumab to be withheld if for first-occurrence Grade 3 event and permanently discontinued if:
  - Grade 3 event recurs
  - Pemetrexed
  - Pembrolizumab or nivolumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥12 weeks
  - Concur to encourage physical activity
  - Anticipatory guidance on proper administration
  - Assess patient & family understanding of recommendations and rationale
  - Identify barriers to adherence

**Implementation:**
- Identify high-risk individuals and those with underlying autoimmune dysfunctions
- Educate patients who arthritis and arthritis are the most commonly reported rheumatic and musculoskeletal IAEs with checkpoint inhibitors
- Arthritis-like symptoms can range from mild (manage as redness, joint pain, and swelling in joints) to severe and severe (ranging multiple immunosuppressant medications)
- Anticipate that the stem cell treatment to manage arthralgia be much higher (i.e., up to 1.5 mg/kg/day) than typically required to manage “classical” inflammatory arthritis
- Educate patients that symptoms can persist beyond treatment completion or discontinuation

**Red Flags:**
- Risk of fall due to mobility issue

**Care Step Pathway - Arthralgias and Arthritis**