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Management of rheumatic complications of immune checkpoint inhibitor therapy – an oncological perspective

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Abstract

Immune checkpoint inhibitors (CPIs) are an effective treatment for many cancers but cause diverse immune-related adverse events (IrAEs). Rheumatological IrAEs include arthralgia, arthritis, tenosynovitis, myositis, polymyalgia rheumatica and sicca syndrome. CPI use can unmask RA as well as causing flares of prior autoimmune or connective tissue disease. Oncologists categorize and grade IrAEs using the Common Terminology Criteria for Adverse Events and manage them according to international guidelines. However, rheumatological events are unfamiliar territory: oncologists need to work with rheumatologists to elicit and assess symptoms, signs, results of imaging and autoantibody testing and to determine the use of steroids and DMARDs. Myositis may overlap with myasthenic crisis and myocarditis and can be life-threatening. Treatment should be offered on balance of risk and benefit, including whether to continue CPI treatment and recognizing the uncertainty over whether glucocorticoids and DMARDs might compromise cancer control.

Key words: immune checkpoint inhibitor, nivolumab, pembrolizumab, ipilimumab, melanoma, NSCLC, arthritis, arthralgia, immune related adverse events, myositis

Rheumatology key messages

- Immune checkpoint inhibitors, used to treat people with cancer, can cause diverse rheumatological adverse events.
- Rheumatological immune-related adverse events should be managed using published oncological guidelines in collaboration with a rheumatologist.
- Decisions on immunosuppression and stopping immunotherapy should balance benefits against uncertain effects in cancer control.

SUPPLEMENT

Introduction

The immune checkpoint inhibitors (CPIs) disrupt signalling pathways that inhibit immunity against cancer. Various agents have distinct mechanisms and possibly diverse cellular targets. Broadly, CTLA4 inhibition enhances the generation of new T cell responses, whereas blocking PD-1 interactions releases activated T cells from inhibition at tissue sites [1–3]. Agents funded in the UK include ipilimumab (targeting CTLA-4), pembrolizumab and nivolumab (PD-1), and avelumab, atezolizumab and durvalumab (PD-L1) are approved for lung, urothelial, renal cell, Merkel cell and head and neck carcinomas, melanoma and Hodgkin's disease, as either palliative or adjuvant therapies. CPIs improve cancer outcomes, including survival, compared with chemotherapy [4–8].

Immune-related adverse events (IrAEs) caused by CPIs may affect any organ and can be life-threatening or life-changing [9, 10]. Most CPI-treated patients experience IrAEs, while the incidence of severe or life-threatening toxicities is 7–20% for anti-PD-1, 10–30% for anti-CTLA4 and >50% for the combination [11–16]. Patients may experience multiple IrAEs [9]. However, their efficacy in otherwise fatal conditions means patients commonly accept the risk of harm from CPIs.

In oncology trials and practice, IrAEs are described using the common terminology criteria for adverse

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events (CTCAE) [17, 18], grading severity as asymptomatic observations not requiring intervention (G1); moderate events affecting instrumental activities of daily living (ADL) such as shopping, requiring limited intervention (G2); severe, medically significant events limiting self-care ADL or requiring hospitalization (G3); life-threatening events (G4) or death (G5). Oncologists follow internationally recognized guidelines for managing IrAEs, which emerged by multidisciplinary consensus without prospective trials [11, 19]. Treatment pathways are linked to CTCAE, which was not designed for this purpose [17, 18]. CTCAE includes terms like arthralgia, arthritis, back pain, fibrosis, joint effusion, decreased range of motion, myalgia, myositis, dry mouth and dry eye, whereas syndromes such as RA, PMR and GCA are omitted.

In CPI trials, rheumatological IrAEs may be underreported because of poor recognition of symptoms [18]. Exclusion of patients with prior rheumatological conditions limits assessment of risk of CPI-induced exacerbations. Retrospective case series of rheumatological IrAEs include the terms arthralgia, arthritis, tenosynovitis, *de novo* and recurrent RA, PsA and seronegative arthritis, PMR, myositis, SS and eosinophilic fasciitis, with an overall incidence of 3.5–13% [20–25]. The incidence appears higher for the anti-CTLA4 and PD-1 combination than for anti-PD-1 monotherapy [20, 22, 24, 26]. Most series of rheumatological IrAEs describe at least half of the cases as also having other IrAEs. The median time for the first rheumatic IrAE is reported as 3–12 months, with wide ranges [20, 22, 27], later than for other IrAEs [21, 26] except in a series selecting patients with more severe presentations [24] or for exacerbations of pre-existing autoimmune conditions [20].

This review summarizes oncological practice in relation to rheumatological IrAEs as a guide to oncologists and to inform rheumatologists of events upstream of referral. Clinical patterns of rheumatological IrAEs collated from case reports and series have recently been comprehensively reviewed [25] and examples are listed in Table 1: here we focus on arthritis, PMR, myositis and inflammatory sialadenitis. Key issues include recognition of life-threatening events, offering CPI to people with prior rheumatological conditions, stopping CPI for IrAEs, using glucocorticoids and immunosuppressive DMARDs and whether these agents affect CPI efficacy and cancer progression.

Clinical patterns of rheumatological IrAEs

Systematic review of 35 CPI cancer trials reported a median incidence of arthralgia of 8% (anti-PD-1 or anti PD-L1), 5% (anti-CTLA-4), 11% (anti-CTLA4 plus PD-1) and 19% (CPI plus chemotherapy) *vs* 9% for comparator chemotherapy arms [28]. A French registry of grade (G) $\geq$2 IrAEs in 908 CPI-treated patients, identified 2 with RA, 2 with PsA and 6 seronegative arthritides (total incidence 1.2%) possibly more common for combination than monotherapy. In a single-centre study, 11/400 (2.8%) developed G2–3 arthritis [21]. CPI-induced inflammatory monoarthritis, oligoarthritis (four or fewer joints), tenosynovitis and polyarthritis are all described, affecting shoulders, knees, feet, wrists, fingers, elbows, spine and hips, with or without associated back pain. Arthritis typically affected large joints or both small and large joints, but it seems unusual to be confined to small joints [24–27]. One series reported symmetrical joint involvement for more than half of patients [22] and another that symmetrical joint involvement was a feature of seropositive and seronegative arthritis but not PsA [24]. One series included three patients with prior PsA, all of who had flares of joint inflammation and skin manifestations on treatment with anti PD-1 [24]. Cases resembling reactive arthritis presented with large joint oligoarthritis (and dactylitis in one) with urethritis and conjunctivitis [29]. Progressive Jaccoud's arthropathy, non-inflammatory swan-neck finger deformities associated with SLE, developed in one case concurrently with uveitis 12 weeks after initiating nivolumab [30]. Small joint involvement with oedema of the hands and feet raises the possibility of remitting seronegative symmetrical synovitis with peripheral oedema (RS3PE) syndrome [31].

RA is a polyarthritis affecting any synovial joint, particularly the extremities, sometimes with extra-articular manifestations, notably interstitial lung disease [32], seropositive in 60–80% of cases for RF and/or anti-cyclic citrullinated peptide or ACPA antibodies [33]. RF and ACPA-positive RA, presenting after CPI treatment with symmetrical proximal and distal polyarthritis and no or non-specific prior history of polyarthritis, is well described in case series. Some patients were demonstrably ACPA positive prior to CPI induction [21, 22, 24, 34]. However, most patients with CPI-induced arthritis were negative for RF and ACPA [27], despite a CPI-induced inflammatory arthritis population reportedly having a higher frequency of RA-associated HLA-DRB1 'shared epitope' alleles [35]. This suggests that for some patients, CPI treatment unmasks a predisposition to RA whereas for most others the mechanism is different, either independent of or mediated through novel autoantibodies.

PMR is a clinical diagnosis characterized by persistent aching in the neck and shoulder and pelvic girdles with morning stiffness, sometimes with systemic features including mild peripheral arthritis and dorsal oedema. Examination typically reveals active and sometimes passive movements limited by pain. Inflammatory markers (CRP, ESR) are elevated but there are no diagnostic autoantibodies. Imaging findings of shoulder subdeltoid bursitis and biceps tenosynovitis could be features of RA or PMR [36, 37]. The incidence of PMR meeting recognized diagnostic criteria is described as 0.2–2% in large retrospective series of CPI-treated patients [23, 24]. Four confirmed cases from multiple French centres occurred 1–9 months after CPI induction (including monotherapy and combination) and were negative for

RF and ACPA, with one ANA positive. Both *de novo* PMR and flares of pre-existing conditions are recognized [38, 39]. Overlap with sicca syndrome is observed [39]. PMR frequently coexists with GCA. Although GCA appears to be unusual following CPI, cases have been reported presenting with occipital headache, scalp tenderness, jaw claudication, amaurosis fugax with PMR features and high inflammatory markers [40].

Myositis induced by CPI treatment is increasingly recognized from retrospective series and case reports, suggesting underreporting in CPI trials [25, 28, 41]. A large Japanese pharmacovigilance database identified 127 myositis cases among 7604 CPI recipients (1.7%), 10 times higher than linked to other drugs. The median time to onset was 28 days after starting CPI. About one-third of cases presented with features of myasthenia gravis [42]. Myasthenia is characterized by muscle fatigability, early impairment of ocular then bulbar muscles and antibodies against components of the neuromuscular junction, whereas myositis commonly causes stable weakness of proximal muscles with high muscle enzyme levels in the blood. An overlap syndrome manifesting with myasthenic crisis plus myositis affecting bulbar, facial, neck and respiratory muscles, with elevated creatine kinase (CK) and myocarditis, is emerging in CPI-treated patients [25, 43] and this pattern may have higher mortality than for people with myositis alone [44]. Outside the CPI context, this overlap occurs infrequently, and many patients also have other autoimmune conditions [45].

In general rheumatological practice, inflammatory myopathies appear to cluster into five clinical entities linked to muscle biopsy and autoantibody patterns [46, 47]. DM is characterized by slow-onset proximal muscle weakness, myalgia, pruritus, periorbital (heliotrope) rash, red lesions on the extensor surfaces of the joints (Gottron's papules), elevated muscle enzymes, myopathic patterns on EMG, MRI appearances consistent with muscle oedema and necrosis and a specific but not sensitive histological appearance on muscle biopsy. DM is described following ipilimumab or pembrolizumab [48, 49]. Immune-mediated necrotizing myopathy is characterized by proximal muscle weakness, exceptionally high muscle enzyme concentrations, myopathic EMG findings and necrosis with minimal lymphocytic infiltration in muscle biopsies. A patient presenting after pembrolizumab with progressive dyspnoea, bilateral ptosis, neck and limb muscle weakness and dysphagia without evidence of myasthenia had pre- and post-mortem histological evidence of necrotic myositis with lymphohistiocytic myocarditis [50]. Another developed proximal weakness, muscular oedema and diffuse rash with very high CK levels and muscular necrosis following ipilimumab and nivolumab combination [51]. Two other cases are reported following pembrolizumab [48]. Overlap myositis is similar to DM associated with other connective tissue diseases. Within this group, detection of autoantibodies against aminoacyl tRNA synthetases associates with particular features, including interstitial lung disease, arthritis, RP, fever or hyperkeratotic radial-finger lesions known as mechanic's hands. A patient developing some of these features after nivolumab is described [52]. Several cases of ipilimumab or anti-PD-1-induced myositis are best described as non-specific myositis or as polymyositis, which includes myositis without features of the other clusters and typically with inflammatory CD8 T cell infiltrates on muscle biopsy. Notably, several have involvement of ocular or bulbar muscles without evidence of myasthenia. One case had proven myositis with normal CK [53–58]. No CPI-induced cases are described that have the unique histological features of inclusion body myositis.

SS is a chronic systemic autoimmune disease mainly impairing salivary, lacrimal and other exocrine gland functions. Secondary SS is a component of other recognized autoimmune syndromes like RA and SLE. Even without these conditions, primary SS can link to an array of extraglandular phenomena, including cutaneous vasculitis, peripheral neuropathy, renal tubular acidosis, pulmonary involvement, lymphoproliferative disease, lymphopenia, anaemia and thrombocytopenia [59]. A French CPI registry found 2/908 patients (0.3%) developed CTCAE G2 SS [24], but dry mouth or eyes may be underrecorded by oncologists. The incidence ranged from 3 to 24% in those CPI trials reporting them [41]. CPI-associated SS is described in a comprehensive clinical, functional and pathological evaluation of 20 consecutive patients referred for dry mouth [60], supported by other case reports [29, 39, 61]. Key features were abrupt onset of symptoms a median of 70 days from the start of CPI, xerostomia that was worse at night or with exercise, sticky thick saliva, dry throat, hoarseness, altered taste, sensitivity to spicy or acidic foods, but parotid swelling or tenderness was unusual. Assessment included for relevant anticholinergic drugs like antidepressants and antihistamines. Signs included altered mucosa on the tongue, gums and palate, including dryness, erythema, papillary atrophy, ulceration and candidiasis but no evidence of oral herpes. Acute dry eye was concurrent in about one-third of patients. Significant salivary hyposecretion was confirmed in nearly all cases (raising the CTCAE grading from 2, based on symptoms alone, to 3) and lacrimal hypofunction in five. Only a few cases were autoantibody positive, some associated with prior conditions. Ultrasonography of major salivary glands showed characteristic features of SS. Pathological evaluation of lip biopsies (for minor salivary glands) revealed patterns ranging from mild non-specific to severe sialadenitis with significant structural damage and included a mild to moderate focal lymphocytic sialadenitis morphologically similar to primary SS. However, whereas primary SS has an infiltrate dominated by $CD20^+$ and $CD4^+$ B and T cells with germinal centre type structures, CPI-associated SS was dominated by PD-1^+ $CD4^+$ and $CD8^+$ cells, few B cells and PD-L1 positivity in the densest infiltrates.

Recognition and initial investigation of rheumatological IrAEs in the oncology setting

Patients receiving CPIs should be asked routinely about musculoskeletal pain, stiffness, dry eyes and mouth, for example, through a pre-clinic questionnaire covering a range of IrAEs. Morning stiffness—difficulty moving joints that eases over time (a typical duration of 1 h is cited as being diagnostic)—is a key but variable symptom of inflammatory arthritis, although it can also be a feature of OA and non-inflammatory widespread pain conditions such as fibromyalgia. The quality or severity of stiffness in addition to the duration and impact on ADL may be informative on the underlying process [62, 63]. Muscle weakness, dyspnoea and dysphagia may be presenting symptoms of myositis.

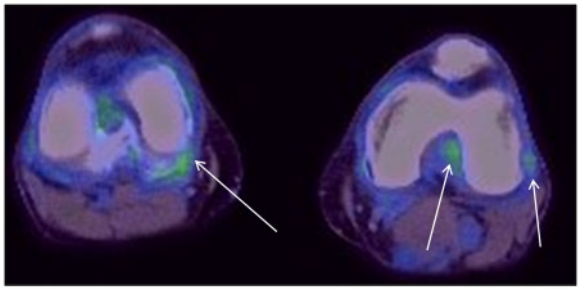
In a patient with musculoskeletal pain, examination should include peripheral joints and the entheseal tissue between tendons, ligaments and bones, looking for arthritis and tenosynovitis. Small-joint synovitis is challenging to detect for inexperienced observers, potentially delaying its recognition by oncologists [26]. Examination should also include looking for muscle pain and strength for evidence of myositis. Muscle fatigability or fluctuating weakness and ocular or bulbar involvement might suggest concurrent myasthenia with myositis. Clinical features of IrAEs need to be distinguished from common, chronic non-inflammatory causes of musculoskeletal pain that can affect up to 25% of adults and account for up to 30% of GP appointments in the UK [64]. Bone or soft tissue metastases may present with symptoms mimicking a rheumatological condition.

For patients presenting with CPI-induced musculoskeletal symptoms, core blood tests are CRP, serum urate, ANA, RF, ACPA and muscle enzyme levels (CK, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase and aldolase). Testing a wider panel of autoantibodies might be reserved for high clinical suspicion of a specific syndrome with specialist advice. Although HLA-B27 associates with AS, reactive arthritis and PsA [65] and is sometimes positive in patients with CPI-induced arthritis [22, 27], its diagnostic value remains unclear in this setting.

Current guidelines suggest the use of joint ultrasound with or without MRI of affected joints to exclude metastases or sepsis, evaluate joint damage and clarify the diagnosis to aid decision making about intervention [19]. MRI scanning of joints appears to have a high detection rate for synovial thickening, oedema, hyperenhancement and joint effusion in people with rheumatic IrAEs [22]. Ultrasound demonstrates synovial thickening and, importantly, increased synovial vascularity in the power Doppler mode [66].

Large joints and the axial skeleton are included on routine oncological imaging: synovitis can be detected on CT or as increased fludeoxyglucose uptake on CT/PET, with PET somewhat more sensitive (Fig. 1) [22, 27]. In one patient with sacroiliitis, increased metabolic activity in the abdominal fascia indicated fasciitis [67]. One series used imaging where available to discriminate patients with prior OA from others with clinical and radiological evidence of *de novo* inflammatory arthritis. Those with prior OA were noted to be older and have fewer joints involved and a higher rate of other IrAEs [22].

Fig. 1 Evidence of rheumatological IrAEs may be observed on scans requested by oncologists



In this example, PET-CT for a patient with melanoma previously treated with anti-PD-1 therapy, requested to investigate for possible oncological relapse, showed peri-articular uptake in both knees (arrows), with associated effusions, and consistent with known synovitis triggered by anti-PD-1 therapy.

Guidelines indicate rheumatological referral for patients with symptoms that limit instrumental ADL, persisting beyond 4 weeks or in whom there is consideration of treatment with systemic glucocorticoids or DMARDs. Referral might also be for joint aspiration and intra-articular corticosteroid therapy for mono- or oligoarthritis or for temporal biopsy for suspected GCA. Synovial fluid aspiration can confirm inflammatory arthritis in the context of CPI treatment, with elevated levels of white cells, but may have a more important role in excluding sepsis. Crystals on polarized light microscopy of synovial fluid might confirm a diagnosis of gout or pseudogout.

If clinical evaluation and muscle enzyme levels suggest myositis with weakness and especially functional loss, urgent rheumatology and neurological referral is required, including for EMG, myositis-associated autoantibodies, MRI or ultrasound imaging for muscle oedema or necrosis and possibly muscle biopsy [46, 48, 55]. High-sensitivity troponin levels should be measured for concurrent myocardial damage. Concurrent myocarditis merits a cardiology referral and cardiac functional imaging [41, 68]. Presentation with fluctuating weakness and ocular or bulbar involvement might suggest myositis overlapping with myasthenia, indicating testing for antibodies for acetylcholine receptor and other components of the neuromuscular junction. Myositis, particularly overlapping with myasthenia, can present with respiratory failure and pulmonary function tests should be performed [25].

Intervention for rheumatological IrAEs

Oncologists follow internationally recognized guidelines for managing IrAEs linked to CTCAE, which emerged by

Table 1 Examples of case series reporting rheumatological IrAE

Author	Year	n	Rheumatic IrAE	Investigations	Treatment	CPI management
Le Burel [24]	2017	17	Selected as grade ≥2 (24): SS (4) with cryoglobulinaemic vasculitis (1), RA (3), myositis (3), PMR (4), PsA (3), seronegative polyarthritis (7). G2 (17), G3 (6)	Serology negative (15). Serology positive: SS—various RF, ACPA, ASSA, ASSB, AENA, ANA, (4/4); RA—RF, ACPA (3/3); myositis—ANA (1/3); PMR—ANA (1/4)	Steroids (20/24): SS (1/4), RA (3/3), myositis (3/3), PMR (4/4), PsA (3/3), polyarthritis (6/7); high dose—1 mg/kg ± bolus for SS (1/4), myositis (3/3), PMR (1/4), polyarthritis (1/7). MTX (3), IVIG—myositis (2/3)	CPI stopped (8/24): myositis (3/3), SS (2/4)
Buder-Bakhaya *et al.* [22]	2018	26	Selected for new arthralgia: shoulders (61.5%), knees (50%), feet (42.3%), wrists (38.5%), fingers (26.9%), spine (19.2%), elbows (15.4%), hips (11.5%). Large joints only (73.1%), large and small joints (26.9%). Symmetrical (62%). G1 (17), G2 (9)	Positive RF (1), RF and ACPA diagnosed with RA (1); HLA-B27-positive (3/18); joint aspiration—clear fluid with lymphocytes and neutrophils (2); imaging showed prior OA (5), MRI showed synovitis (4/7), PET showed synovitis (5/6)	NSAIDs only (19/26); prednisolone 5–10 mg/day (5/26); high-dose steroids for seronegative arthritis (1/26); SSZ and HCQ for RA	Stopped for PR/CR with resolution of arthritis (4); stopped PD or toxicity (9) with ongoing arthritis (1); continued CPI (13) with ongoing arthritis (8) requiring NSAIDs and/or steroids (7)
Lidar *et al.* [21]	2018	14	Inflammatory arthritis (12), eosinophilic fasciitis (1), sarcoidosis (1). G2 (4), G3	Negative RF (14) and ANA (14); positive ACPA (1/14), patient clinically had RA	NSAIDs (11) ineffective in all, steroids effective (5), steroids with MTX effective (3), steroids partially effective with MTX (5), steroids partially effective (1)	Stopped (8), withheld (3), continued (3)
Cappelli *et al.* [26]	2018	30	Referred to rheumatology for inflammatory arthritis: affecting knee (17), other large joints (7), small joints (6); median swollen joints 7; reactive arthritis triad (3)	Positive ACPA (1), RF (1), ANA (2)	Corticosteroids (20), prednisolone median dose 40 mg (20–60), MTX (3), anti-TNF (7), persistence of symptoms >3 months (18/21)	At least 21 stopped CPI and 18/21 had ongoing symptoms >3 months after stopping
Leipe *et al.* [27]	2018	16	Referred to rheumatologist for new-onset rheumatic IrAEs. Arthritis—mono (7), oligo (5), poly (2); plus PMR (5), xerostomia (2), xerophthalmia (1), myositis (1)	Synovial fluid ≥2000 white cells/mm^3 (4/4). Positive low-titre RF (5), ACPA (1), ANA (9), ASSA positive with xerophthalmia (1), B27 (0/10). Musculoskeletal inflammation shown on US (10), PET (5), CT (5), MRI (4)	NSAIDs only for arthralgia (2) and arthritis (2); IA steroids (8), oral steroids 20–30 mg (7), MTX 15 mg/week for flare on taper (6), SSZ (1)	None stopped for rheumatological IrAEs
Liew *et al.* [20]	2019	19	Inflammatory arthritis (16), PMR (3). Seven patients had prior arthritis or PMR, 12 *de novo* events. G1 (7), G2 (11), G3 (1)	Positive RF (1/13) and ACPA (1/10); objective finding on imaging (11)	Prednisolone (15) doses not specified; DMARD (4) not specified	Stopped (3)

ASSA, anti-SS-related antigen A/Ro; ASSB, anti-SS-related antigen/La; AENA, anti-extractable nuclear antigens; CR, complete response; IA, intra-articular; PD, progressive disease; PR, partial response; SD, stable disease.

multidisciplinary consensus without prospective trials [11, 19]. US guidelines detail examination, investigation and intervention across three musculoskeletal categories: inflammatory arthritis, myositis and PMR-like syndrome [19].

For arthritis, grade 1 symptoms can be managed with paracetamol and NSAID use alone (unless contraindicated). In case series (Table 1), the use of NSAIDs has been reported as being effective, particularly for arthralgia [22], and ineffective [21]. This variation may be an effect of different approaches to case identification. Guidelines advocate prednisolone 10–20 mg/day for CTCAE G2 events and prednisone 0.5 mg/kg for G3 (i.e. significantly limiting function). In view of dose-related metabolic AEs of corticosteroids [69], the aim should be to control symptoms with low doses and taper to significantly less than a prednisolone equivalent of 10 mg/day. In case series (Table 1), there is no standard steroid dosing, ranging from a prednisolone equivalent of 10–60 mg/day. For acute monoarthritis, an intra-articular steroid injection can be rapidly effective [27]. This might be less immunosuppressive than systemic glucocorticoids, but there is clearly a systemic effect evidenced in suppression of the hypophysial–adrenal cortisol access [70].

Conventionally, rheumatologists treat RA with early introduction of DMARDs early to modify the later disease course [32]. However, it is uncertain if these principles apply to the management of CPI-associated inflammatory arthritis. Oncology guidelines suggest escalation to DMARDs following symptom flare on tapering of higher doses or if there is no resolution within 4 weeks rather than escalating steroid doses. First-line conventional DMARDs for RA and the 'anchor' drug of combination therapy is MTX, with alternatives including SSZ and LEF. HCQ is rarely used as monotherapy, except in mild or palindromic cases, but it is useful as an 'add-on'. MTX is used for CPI-associated inflammatory arthritis, typically for symptom flare on steroid taper or prolonged partially responding symptoms on glucocorticoids. One study reported that early introduction of MTX was associated with high levels of remission [27]. In one series, anti-TNF was used more than MTX for patients with persistent symptoms on glucocorticoids [26]. The use of SSZ and HCQ is mentioned for individual patients [22, 27]. However, we observed a high frequency of AEs to SSZ following anti-PD-1 therapy, which may be T cell mediated [71]. LEF is mentioned as an alternative DMARD for inflammatory arthritis in the American Society of Clinical Oncology (ASCO) guidelines, but with little reported experience of its use. Tocilizumab has been used successfully for IrAE arthritis [72], although the ASCO guidelines caution against its use in patients with concomitant colitis [19].

First-line management of PMR, outside of a CPI context, is lower dose glucocorticoids, weaned down over 12–24 months [73], with second-line agents used less commonly. For inflammatory sialoadenitis, sicca or SS, supportive measures include artificial saliva and cholinergic agonists, good oral hygiene and recognition and treatment of candidiasis. In a recent series [60], 12/20 stopped or suspended CPI treatment and 10 had systemic prednisolone ranging from 10 to 80 mg. There was a variable response to glucocorticoids and no complete resolution systematically or on functional testing.

For myositis, IrAE guidelines advocate initiating prednisone or equivalent 0.5 mg/kg for G2 symptoms and CK greater than three times the upper limit of normal, at 1 mg/kg for a G3 event, and 1–2 mg/kg of methylprednisolone or a higher-dose bolus for weakness severely limiting mobility, or with cardiac, respiratory or bulbar involvement, as well as appropriate inpatient supportive care. Subsequent lines of treatment include plasmapheresis and IVIG, which come from neurological practice for treating severe autoimmune events. A mechanistic understanding supporting these approaches in this setting is lacking.

Prior autoimmune conditions and CPI treatment

Systematic review identified 123 CPI-treated patients with diverse pre-existing autoimmune disease, active in 46% and on treatment in 44%. Half experienced an exacerbation on CPI and one-third had *de novo* IrAEs. This was unrelated to whether prior disease was active and the frequency of events was lower for those on treatment for prior autoimmune disease at the start of CPI. At least half of patients experienced an exacerbation of RA (10/20 with arthritis flare) or psoriatic disease (22/28 mainly cutaneous flares) [74]. A series identified 52 melanoma patients treated with anti-PD-(L)1 who had prior autoimmune diseases including RA, PsA, IBD and neurological conditions, of whom 15 had ongoing symptoms and 20 had current immunosuppression [75]. Of these, 20 (38%) had a disease flare on starting CPI, including half those with RA. Almost all events were G1–2 and required oral glucocorticoids with or without steroid-sparing agents, with no use of high-dose glucocorticoids or anti-TNF. The median time of onset from starting CPI was 38 days (range 8–161). This supports observations made by others of earlier onset of rheumatological IrAEs for those with pre-existing disease and possibly a family history of connective tissue or autoimmune diseases [20, 76]. The authors' practice is that CPI treatment for cancer can be given to people with prior autoimmune and inflammatory conditions, balancing risk and benefit for each individual. It is likely but not definite that CPI treatment will cause an exacerbation of the prior inflammatory condition, and collaboration with a rheumatologist from start of CPI treatment is advised.

Effect of immunosuppression on cancer control

Glucocorticoids inhibit the function of Th1, Th2 and Th17 T lymphocytes, macrophages, pro-inflammatory dendritic cells and neutrophils and enhance the function of regulatory T cells and tolerogenic dendritic cells [77] and might reduce the efficacy of CPI. A review of ipilimumab-treated patients with melanoma showed no impact on survival for the one-third subsequently

receiving glucocorticoids for IrAEs [78]. The response rate for nivolumab-treated patients was higher for patients experiencing IrAEs than not and similar between those who did and did not receive immunosuppressing agents [10]. There is an observation of better disease control and survival for those with rheumatological IrAEs compared with the whole CPI-treated cohort [20, 22]. While reassuring about using glucocorticoids to treat rheumatological IrAEs, there are interacting factors affecting outcomes in these studies.

In contrast, for lung cancer patients, prednisolone equivalent >10 mg/day when starting anti-PD1 associated with worse progression-free and overall survival (PFS and OS), even accounting for performance status and brain metastases [79]. A separate study suggested patients have better outcomes if exposed to glucocorticoids only later in CPI treatment [78]. For patients with prior autoimmune conditions, the tumour response rate was much lower for people on immunosuppressant agents at the start of CPI (15% *vs* 44%) [75]. These suggest a time-sensitive negative effect of glucocorticoids and immunosuppressants on CPI efficacy. It is plausible that for an individual, minimizing steroid exposure, especially at the start of CPI treatment, might improve long-term tumour control as well as limiting metabolic adverse events [69] and risk of infection.

Oncologists know MTX as a folate antagonist cytotoxic agent. Used as a DMARD, doses are lower (up to 20–25 mg/week) with folate and probably modify T cell signalling [80]. There is a possible association between RA, MTX use and cancer risk, for example, in registry and case–control studies in relation to melanoma or lung cancer [81–84]. These do not prove causality, but are concerning in that prolonged MTX for IrAEs could reduce cancer control. Australian studies found that relative to the general population, MTX-treated RA patients had a higher risk of cancer, including Hodgkins disease, melanoma and lung cancer [85], but no additional risk from biologic agents, including anti-TNF [86]. Initial concerns over risks of invasive melanoma from the use of anti-TNF and other biologics were not borne out by a large study incorporating 11 European biologic registers [87], nor in a meta-analysis of papers reporting cancer recurrence in patients with RA and IBD, although recurrence rates were numerically higher for those on combination immunosuppression [88]. TNF has a complex relationship with cancer progression, with studies implicating both TNF signalling and its loss in immune evasion [89, 90] and there is an ongoing clinical trial of anti-TNF in combination with CPI in melanoma (NCT03293784). Immune networks are complex, and diverse immunosuppressive monoclonal antibodies and immune signalling inhibitors [89–91] might have varied effects on CPI efficacy against malignancy. Our recommendation is to offer glucocorticoids and DMARDs, with rheumatological supervision, if these are required to control IrAEs, but to proactively minimize exposure to immunosuppressants at initiation of CPI treatment or as maintenance following IrAEs.

Continuing the CPI after an IrAE

Across all IrAEs, the general principle is to continue CPI treatment for G1 events, suspend for G2 until resolution to G1 and terminate treatment for G3 or 4 severe or life-threatening events [19]. CPI treatment would be stopped permanently after myositis with myocarditis or respiratory impairment, and possibly for non-life-threatening myositis, to reduce the risk of life-threatening events. For other rheumatological events, CPI might be restarted after resolution, even of severe events, in consultation with a rheumatologist, balancing quality of life against the priority to control malignancy.

Case series show individualized decisions being made: ceasing CPI or continuing, with or without ongoing immunosuppression and anti-inflammatory agents (Table 1). Patients with myositis did not continue CPI treatment [24]. Series vary in whether patients stopping CPI had subsequent resolution of arthritis [22, 26]. Recurrence of rheumatological IrAEs in patients recommencing CPI is documented [20]. Generally, in a lung cancer cohort, around half of patients re-treated after any IrAEs had a recurrence or a different IrAE. While 54% were G1–2 and 84% resolved, 2 of 38 died. Restarting CPI associated with better PFS and OS for those who had not reached response at the time of the IrAE, but not for those with an early tumour response [92]. For melanoma patients treated with ipilimumab and nivolumab, there was no obvious detriment to tumour outcomes comparing patients with or without an IrAE that required cessation during the induction phase. Responses continued to occur after discontinuation [93]. However, these treatment-limiting IrAEs were severe or life-threatening, different from most rheumatological IrAEs. The two cohorts differed in baseline characteristics and follow-up was short, leaving ongoing uncertainty about long-term effects of stopping *vs* continuing CPI after an IrAE. In summary, the decision to continue or restart CPI in relation to a rheumatological IrAE has to be individualized, balancing cancer control, particularly if responses to CPI are still evolving, against life-threatening consequences or impairment of quality of life from IrAE flare.

Conclusion

Effective management requires increased awareness among oncologists, with access to relevant education and a close working relationship with rheumatologists experienced in the management of inflammatory musculoskeletal IrAEs. Myositis can be life-threatening, including muscle necrosis, respiratory compromise and myocarditis, and early intervention is essential. Non-life-threatening rheumatological IrAEs are still debilitating and should be actively managed according to both oncological guidelines and standard rheumatological practice. It is uncertain that glucocorticoids and DMARDs for IrAEs compromise cancer outcomes: they should be used as required and exposure minimized if

possible. It is reasonable to offer CPI treatment to people with prior autoimmune diseases and to restart CPI after an IrAE is controlled, balancing the risk of life-threatening recurrence against maximizing the chance of cancer control.

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