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Management of rheumatic complications of ICI therapy: a rheumatology viewpoint

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Abstract

Since immune checkpoint inhibitors became the standard of care for an increasing number of indications, more patients have been exposed to these drugs and physicians are more challenged with the management of a unique spectrum of immune-related adverse events (irAEs) associated with immune checkpoint inhibitors. Those irAEs of autoimmune or autoinflammatory origin, or both, can involve any organ or tissue, but most commonly affect the dermatological, gastrointestinal and endocrine systems. Rheumatic/systemic irAEs seem to be less frequent (although underreporting in clinical trials is probable), but information on their management is highly relevant given that they can persist longer than other irAEs. Their management consists of anti-inflammatory treatment including glucocorticoids, synthetic and biologic immunomodulatory/immunosuppressive drugs, symptomatic therapies as well as holding or, rarely, discontinuation of immune checkpoint inhibitors. Here, we summarize the management of rheumatic/systemic irAEs based on data from clinical trials but mainly from published case reports and series, contextualize them and propose perspectives for their treatment.

Key words: management, treatment, rheumatic immune-related adverse events (irAEs), cancer immunotherapy, immune checkpoint inhibitors

Rheumatology key messages

- Treatment should be chosen according to intensity and entity of rheumatic/systemic irAEs.
- Glucocorticoids are effective but should be tapered ideally <10mg; if required, csDMARDs/bDMARDs should be applied.
- Management of rheumatic/systemic irAEs aims to pursue ICI-treatment; rarely, discontinuation of ICI is required.

SUPPLEMENT

Introduction

Owing to their non-specific mechanism of activating T cells, immune checkpoint inhibitors (ICIs) are accompanied by a wide spectrum of toxicities due to inflammatory autoimmune tissue damage. These toxicities—referred to as immune-related adverse events (irAEs)—can potentially affect every organ system; however, the dermatological, gastrointestinal and endocrine systems are most commonly affected [1]. The mainstay of treating these irAEs is glucocorticoids, usually given for a limited time of about 4–6 weeks, depending on clinical presentation and severity. Whereas most (non-rheumatic) irAEs resolve within weeks to months of treatment and glucocorticoids can be stopped, a small subset of patients requires the add-on of other immunomodulatory or suppressive agents (e.g. the TNF-inhibitor infliximab used in ICI-related colitis) [1, 2]. For severe symptoms (⩾ grade 3 by Common Terminology for Adverse Events grading, a set of criteria for the standardized classification of adverse effects (AE) of drugs used in cancer therapy; a grading is provided for each AE term), ICIs may also be held or discontinued.

In large clinical trials, primarily rheumatic symptoms (e.g. arthralgia and myalgia) and with a rather low incidence (⩽1%) also a few rheumatic/systemic irAEs (particularly arthritis and myositis) have been described [1]. However, there is the suspicion that rheumatic/systemic irAEs are underreported in clinical trials. Indeed, many clinical trials do not report rheumatic irAEs (disregarding musculoskeletal/rheumatic/systemic events as a distinct

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organ system, even in the supplemental data), do not provide clinical descriptions of rheumatic irAEs, or only report high-grade adverse events and frequent events (occurring in $\geqslant$10% of the patients), thus potentially even excluding events such as inflammatory arthritis. Conversely to clinical trials, prospective observational data demonstrate an incidence of ~5% of *de novo* rheumatic/systemic irAEs.

As a consequence, descriptions of rheumatic/systemic irAEs are mainly derived from case reports and series. The abundance of rheumatic symptoms and irAEs differed between the combination of anti-PD1/PDL1 and anti-CTLA 4 *vs* monotherapies. Clinical trials of metastatic melanoma showed that the combination of anti-CTLA 4 and anti-PD1 (ipilimumab and nivolumab) compared with respective monotherapies was associated with higher frequencies of arthralgia (10.6% *vs* 6.4 and 6.4) and myalgia (2.2% *vs* 1.7% and 1.1%) [1]. However, true rheumatic/systemic irAEs were much more frequently reported for patients with anti-PD1/PDL1 antibodies (~75% of these irAEs) followed by the combination of them with anti-CTLA4 antibodies (~20%) than with anti-CTLA4 antibodies alone (~5%).

Rheumatic/systemic irAEs reflect the large spectrum of known rheumatic diseases and include arthralgia/arthritis, enthesitis, PMR, myalgia/myositis, sarcoidosis (-like), systemic sclerosis (-like), Sjögreńs (-like)/sicca syndrome, lupus (-like) and vasculitis. These irAEs have been predominantly described in patients *de novo* without pre-existing autoimmune disease, which is the focus of this article. However, rheumatic and systemic irAEs were also recently reported for patients with pre-existing autoimmune disease, mostly as a flare or worsening of the known rheumatic disease (~40% of patients) or other types of irAEs (~35% of patients) [3–20]. Because those increases in disease activity can usually be managed well, a pre-existing autoimmune disease is not a contraindication and should not preclude the use of checkpoint inhibitors.

Rheumatic and systemic irAEs have been characterized and reviewed systematically [1, 2, 21–24]. Yet the diagnostic and therapeutic approaches vary greatly and data on efficacy and safety of their management have been reported less systematically. However, since—unlike other irAEs—rheumatic irAE can persist for longer time periods even after ICIs are discontinued, information on the management is highly relevant [2].

Here, we review the management of rheumatic and systemic irAEs based on the information available from the case reports and series. Regarding the efficacy of treatment, an objective response (e.g. based on disease activity scores) cannot be consistently derived from case reports, mainly due to the heterogeneity of irAEs (e.g. mono- oligo- or polyarthritis) and the observation that they do not fully resemble classic rheumatic diseases (e.g. low CRP in some cases of PMR [-like] disease). Therefore, the information given in this review is largely based on qualitative information included in the reports. By additionally providing a personal perspective based on the experience in treating rheumatic and systemic irAEs, we want to aid decision making for their management.

Recent data have emerged suggesting that occurrence of irAEs in general [25] and specifically also of rheumatic irAEs [26–28] might be of good prognosis for getting an effective anti-tumour response with ICI. Thus, an appropriate management of these rheumatic/systemic IrAEs is crucial for allowing the oncologist to pursue ICI if they are efficient against cancer. On the other hand, a concern of immunomodulatory treatment of irAEs is a potential negative effect on the anti-tumour response of ICIs due to damping of the immune response.

Therefore, in this article, we discuss the management of common rheumatic and systemic irAEs as well as their impact on the anti-tumour response.

Management of peripheral arthritis

Peripheral arthritis may take different forms [26, 28–50]. Symmetrical RA-like arthritis may occur most frequently seronegative, but true cases of seropositive RA have been reported (some of these cases having pre-existing autoantibodies without any symptoms). Other cases present with asymmetrical arthritis sometimes associated with psoriasis or only arthralgia.

In the published cases with ICI-induced arthritis ($>$200), the management of arthritis included treatment with NSAIDs, glucocorticoids (systemic and intra-articular), conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs, a term developed for RA) and biological DMARDs (bDMARDs, a term developed for RA) (Table 1), but also discontinuation of ICI therapy.

About one-fifth of patients with ICI-induced arthritis received NSAIDs, often as first line treatment in rather mild forms of arthritis. However, inefficacy was reported in ~40% of those cases. The insufficient response in many patients might be due to the fact that even mild forms of arthritis often require more potent immunomodulatory treatment. In many cases, the rationale behind the choice for NSAIDs as first-line treatment (over glucocorticoids, for example) seems to avoid immunosuppression that might potentially interfere with anti-tumour immune response.

The majority of the patients with arthritis received systemic glucocorticoids (~2/3) with an initial dose of around 15–20 mg prednisone equivalent. However, the glucocorticoid dose varied from low, moderate to high doses, with most patients receiving moderate doses starting with 20 mg prednisone. Sometimes, the dose was higher, up to 40 mg/day prednisone.

Overall, it seems that the glucocorticoid dosage was chosen based on the severity of arthritis. In virtually all patients, signs and symptoms of arthritis were controlled by glucocorticoid treatment. If not controlled by the start dose, an increase of glucocorticoid dose was usually effective. Additionally, about 15% of patients received intra-articular glucocorticoid injections, in most cases with a good response. Still, those local treatments seem only reasonable in patients with mono- or oligoarthritis, in whom only one or a few joints need to be injected.

In the majority of patients, glucocorticoids could be successfully tapered. The duration of tapering varied

Table 1 Treatments proposed in case series for rheumatic/systemic irAEs

	NSAIDs	Gluco-corticoids	csDMARDs (MTX, HCQ, SSZ)	bDMARDs (TNFi, IL-6Ri)	IVIG and/or plasma exchange
Arthritis					
Use	+	+++	++	+	–
Efficacy	+	+++	++	+++	NA
PMR					
Use	–	+++	–	(+)	–
Efficacy	NA	+++	NA	+++	NA
Myositis					
Use	–	+++	+	(+)	++
Efficacy	NA	++	++	+	++
Vasculitis					
Use	–	+++	+	–	–
Efficacy	NA	++	++	NA	NA
Sicca/Sjögren's syndrome					
Use	–	+++	–	(+)	(+)
Efficacy	NA	++	NA	(+)	(+)
Other CTD/ sarcoidosis					
Use	–	++	++	(+)	–
Efficacy			+	++	NA

bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic DMARDs; NA: not applicable; –: if not used; (+): if used in single cases/some efficacy in single cases; +: if used in a few cases/low efficacy; ++: if used in 10–50%/moderate efficacy; +++: if used in >50%/high efficacy (ratings are based on semi quantitative estimates).

individually a great deal between a few weeks to several months and was frequently prolonged when symptoms recurred. When glucocorticoid tapering including discontinuation failed, some patients were continued on low to moderate doses, often with the aim to enable continuation of ICI therapy with tolerable irAE symptom intensity. With regard to safety of glucocorticoid treatment, no severe adverse effects were reported. Although no worsening of tumour or anti-tumour response has been reported, any interpretations regarding a lack of interference must be made with the highest caution.

Of all patients with arthritis, around one-fifth received csDMARDs. The most common csDMARD regimen was methotrexate (~60%), followed by hydroxychloroquine (~25%), hydroxychloroquine/sulfasalazine combination (~15%), sulfasalazine (~5%), methotrexate/sulfasalazine combination (~5%), in some cases administered sequentially. In most cases (~90%), initiation of csDMARDs enabled tapering of glucocorticoids and also symptom control. In one study focusing on ICI-induced arthritis, arthritis control was even achieved in all six MTX-treated patients [42].

Biologic DMARDs were initiated in around one-tenth of patients with ICI-induced arthritis. Among bDMARDs, TNF inhibitors were the most frequently applied (~70%) followed by tocilizumab (~30%) targeting the IL-6 receptor (IL-6R), with one patient not responding to infliximab but tocilizumab. Tocilizumab seemed to be an effective alternative to TNF inhibitors in a recent case series [39]. Taking into account the limitations regarding conclusions about efficacy and safety, as discussed in this article, bDMARDs were highly effective in reducing signs and symptoms of arthritis without safety issues throughout the limited duration of follow-up.

With regard to discontinuation of ICI therapy, in only around one-quarter of the patients, tumour immunotherapy was stopped as a consequence of the ICI-induced arthritis. Although follow-up in case reports was usually limited in time, in most of the patients ICI therapy could usually be reintroduced later when arthritis was controlled.

Of note, re-exposure of ICI treatment is only contraindicated after occurrence of grade 4 (life-threatening) adverse events [20].

In summary, glucocorticoids are effective; however, csDMARD or even bDMARDs should be considered in patients with insufficient response to acceptable doses of glucocorticoids and/or requiring glucocorticoid sparing regimens.

Management of PMR and PMR-like syndromes

PMR/PMR-like syndrome with a clinical presentation of acute predominant bilateral shoulder and/or hip pain and morning stiffness are described complications of ICI therapy (35 published cases) [28, 30, 31, 36, 50–56]. The clinician must be aware that in some cases, inflammation parameters (ESR and CRP) may be normal. Further, like in non-cancer patients, an association with giant cell arteritis was reported [53]. Management of PMR is based on moderate dose glucocorticoids (15–20 mg/day), with an almost invariably good response (Table 1). Of note, it seems that in some cases, higher initial doses of

glucocorticoids are required, or glucocorticoids-dependence is observed when tapering. In glucocorticoid-refractory cases, methotrexate was successfully used. Regarding bDMARDs, anti-IL-6 receptor antibody may be an option [50].

Management of myositis/inflammatory myopathy

In clinical trials, myalgia was the second most commonly reported musculoskeletal complaint (2–21%) of trial participants [57]. Whereas it is speculative that some of these patients might have had undetected myositis/inflammatory myopathy, or PMR-like syndrome, several true cases of inflammatory myositis under ICI therapy have been published including information on their treatment (Table 1) [31, 49, 58–76]. Most of them resembled polymyositis, but also clinical patterns of dermatomyositis, eosinophilic fasciitis, ocular myositis, myasthenia and myocarditis were reported.

The vast majority of patients with myositis received systemic glucocorticoids (~80%), with an initial dose of around 70 mg prednisolone equivalent (frequently ~1 mg/kg body weight) and ~10% received a bolus. The efficacy was generally good, particularly regarding a substantial decrease in creatine kinase levels, but also regarding symptom relief; however, there were also a few cases with insufficient response and mostly fatal outcomes.

Despite the mostly good response to glucocorticoids, prolonged remissions were rarely achieved through monotherapy: during glucocorticoid tapering, disease activity often increased, necessitating – and if not combined already initially – other immunomodulatory treatments. These treatments (analogous to severe or difficult-to-treat classic myositis entities) frequently included intravenous immunoglobulins (~20%), plasma exchange (~10%) and in a few cases infliximab and extracorporeal immunoadsorption. Less frequent glucocorticoid-sparing treatments (~5%) included methotrexate, mycophenolate mofetil, azathioprine and hydroxychloroquine, often combined with intravenous immunoglobulins and plasma exchange.

The efficacy varied from remission with successful tapering of glucocorticoids to fatal outcomes, often depending on the manifestation of myositis.

About 5% of the patients with myositis and concomitant ptosis, opthalmoplegia or myasthenia gravis received pyridostigmine. This treatment frequently resulted in an improvement of extraocular and oculobulbar weakness.

ICI therapy was withdrawn in almost 90% of the cases at least temporarily, often also indefinitely, particularly in patients with the so-called 3 M syndrome—association of myositis, myasthenia and myocarditis—bulbar myopathy respiratory muscle involvement and necrotizing myositis, which were associated with respiratory failure and death.

Overall, treatment of myositis often requires intensive immunosuppressive treatment with high-dose glucocorticoids, in combination with IVIG and/or plasma exchanges and GC-sparing synthetic agents. In patients with mild to moderate myositis, withholding of ICI therapy can be possible, while in patients with severe life-threatening manifestations, discontinuation appears necessary (Table 2).

Management of vasculitis

The clinical spectrum of ~30 cases reporting ICI-induced systemic vasculitis predominantly comprised leukocytoclastic vasculitis resembling granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis (Table 1)

Table 2 Systemic irAEs treatments adapted to stages of severity of rheumatic/systemic irAEs

Severity of rheumatic irAEs	Treatment	ICI therapy
Arthralgia, mild arthritis, tendinitis/enthesitis (e.g. mono-/oligoarthritis- and SpA-like)	NSAID and/or IACS	Continue
Moderate arthritis/ tendinitis/enthesitis; PMR (e.g. mono-/oligoarthritis)	Low-medium dose prednisolone 10-20 mg/d (and/or IACS) +/− analgesics consider csDMARDs[a]	Continue
Severe inflammatory arthritis/ tendinitis/ enthesitis (e.g. oligo-, polyarthritis) Mild myositis Sarcoidosis, scleroderma, sicca syndrome Mild-moderate vasculitis	Medium to high-dose prednisolone 10 mg -1 mg/kg Consider csDMARDs, bDMARDs, (IVIG/ plasma exchange in case of myositis)[a]	Consider with the oncologist holding or continuing
Severe myositis (e.g. with bulbar symptoms) Severe vasculitis (organ-threatening)	High-dose (i.v.) prednisolone 1–2 mg/kg consider bDMARDs, IVIG/ plasma exchange[a]	Stop

[a]In case of severe and/or glucocorticoid-refractory/dependent irAEs. bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic DMARDs; IACS: intra-articular corticosteroids; irAE: immune related adverse event; SpA: spondyloarthritis.

[23, 24, 69, 77–85]. About two-thirds of the patients with small vessel vasculitis received systemic glucocorticoids, with an initial average dose of ~60 mg of prednisone equivalent (initial dose often: 1 mg/kg). Around 15% of the patients, mostly the severe cases, received a glucocorticoid bolus. The reported response particularly regarding vasculitis lesions (e.g. skin, gastrointestinal tract) was good overall.

Whereas giant cell arteritis was reported in one randomized controlled trial without further information regarding the treatment [57], two cases were reported with a good response to 50–60 mg of prednisone [53]. About 15% of patients received csDMARDs. Most frequently hydroxychloroquine, methotrexate and combinations thereof were used for leukocytoclastic vasculitis and seemed to be effective and glucocorticoid-sparing. In a few cases with severe vasculitis, patients received rituximab 375 mg/m^2 or plasma exchange.

The proportion of patients, in which ICI therapy had to be stopped, was high overall (~80%).

Management of sicca/Sjögren's syndrome

Similarly, in the 19 cases of sicca syndrome [31, 57, 69, 86], that has been defined as a distinct rheumatic irAE entity, a high proportion of patients received systemic glucocorticoids (~75%) with an average dose of ~40 mg prednisone equivalent (Table 1). Further, IVIG, cyclophosphamide and rituximab were used in single cases, the latter additionally to bolus glucocorticoid treatment in a patient with neurological manifestation. Symptomatic treatment, pilocarpine (secretagogue) therapy and withdrawal of ICIs lead to partial resolution of sicca symptoms in several cases.

Together, in addition to the use of glucocorticoid treatment, symptomatic/pilocarpine therapy seems to be effective.

Management of other connective tissue disease/sarcoidosis

Systemic glucocorticoids were commonly used in patients with sarcoidosis ~45% (average dose 55 mg/d), with lupus (-like) disease ~45% (most 1 mg/kg), and with scleroderma (-like) disease 100% (1 mg/kg), which was associated with a good response particularly to cutaneous and arthritic manifestations (Table 1) [24, 57, 87–92]. In one patient with ipilimumab-induced lupus nephritis prednisone therapy (1 mg/kg) and discontinuation of ipilimumab resulted in a substantial improvement of the kidney function [93].

Among the csDMARDs, hydroxychloroquine—analogous to non-cancer patients with connective tissue disease—was used most frequently (~60%) in lupus (-like) and scleroderma (-like) disease with at least partial responses, e.g. in skin manifestations. MMF (~30%) was applied to patients with scleroderma(-like) disease, probably because of its antifibrotic effects, and MTX (~15%) in patients with neurosarcoidosis, overall with a moderate to poor response. In contrast, infliximab was successfully used in two patients with neurosarcoidosis [90, 94], consistent with several positive reports in the non-irAE situation [95, 96].

ICI discontinuation was necessary due to several reasons; mainly, organ-threating manifestations in ~65% of patients with sarcoidosis, ~75% of patients with scleroderma (-like) disease and ~80% of patients lupus (-like) disease, respectively.

In summary, the treatment of these diseases is reminiscent of those from the traditional entities with an efficacy differing dependent on the manifestation, ranging from good responses to glucocorticoids (± DMARDs) regarding dermatitis or renal manifestations to poor outcomes regarding sclerotic lesions.

Discussion

Our overview suggests that the management of patients with rheumatic and systemic irAEs in most cases resembles that of traditional rheumatic entities, suggesting that clinicians have treated CPI-induced autoimmune rheumatic diseases like traditional forms of these conditions. This is understandable given the lack of data (particularly from high-quality evidence) and detailed recommendations regarding (optimal) treatment of those irAEs. In this regard, an important limitation is that the interpretation of irAE treatments' efficacy and safety is based on case reports/series (not controlled studies) of a heterogeneous patient population, with a rather short treatment duration and a potential publication bias by reporting cases with rather favourable outcomes. Further complicating the assessment of treatment efficacy, an objective response (e.g. based on disease activity scores) cannot be consistently derived from the case reports, mainly due to the heterogeneity of irAEs (e.g. mono-, oligo- or polyarthritis) and the observation that they do not fully equal classic rheumatic diseases. In fact, the clinical features are atypical in many cases and differ from the traditional forms of these rheumatic diseases. For this reason and other potential issues resulting from evidence derived from case reports/series (e.g. heterogeneous patient populations, short treatment duration, inconsistent reporting of outcomes in the literature and publication bias), readers should consider treatment advice with caution.

Nevertheless, because we are at the beginning of understanding the optimal regimens and implications of adjunctive immunosuppression, publications of rheumatic irAEs and their treatment response within case reports or systematic reviews are of great importance to advance our knowledge of efficacious and safe regimens.

In general, like for traditional rheumatic entities, treatments were mostly chosen according to disease extent and severity (Tables 1 and 2). For arthritis, NSAIDs seemed to be sufficient only in a minority, whereas glucocorticoids required by most patients lead to control of signs and symptoms, and seem to be an efficacious treatment option. After achievement of a good response, successful tapering seems to be possible in the majority of patients. Tapering to the lowest possible dose seems to

be preferable in order to reduce glucocorticoid toxicity in general. This is particularly important for patients at high-risk under glucocorticoid treatment for infections (e.g. the elderly, previous serious infections, comorbidities), diabetic or hypertensive derailments and other adverse events. Importantly, further in favour of reducing glucocorticoid doses are data demonstrating that a dose of $\geqslant$10 mg prednisone equivalent/day at the start of ICI treatment is associated with a significantly poorer anti-tumour response (overall response rate, progression-free survival and overall survival) [97]. However, those data (derived from a study in which patients received glucocorticoids before the initiation and not in the course of ICI treatment) should result in an automatism to stop to ICI therapy when prednisone dose is $\geqslant$10 mg. Nevertheless, given the known potential side effects of glucocorticoids in general, particularly in high-risk patients the target of reaching a prednisone dose $<$10 mg within a few weeks seems to be a desirable approach. A very recent meta-analysis of seven trials of anti-PD1/PDL1 antibodies in urothelial cancers showed that the patients having experienced an IrAE had twice as good a chance of responding to the treatment, without any deleterious role of glucocorticoids [98].

In case of unsuccessful tapering, DMARD treatment seems to be a good option. In the published cases, about one-fifth of the patients needed DMARDs normally as a consequence of increased activity upon glucocorticoid tapering. In contrast, patients with PMR (-like) disease usually responded to glucocorticoid monotherapy, which, it seems, can be tapered as in non-cancer patients. In arthritis cases with glucocorticoid-dependent and/or insufficient response to csDMARD, bDMARD treatment with TNF or IL-6R inhibitors were effectively used. Of note, no evidence of an advantage of one drug over another within csDMARDs or bDMARDs has been shown yet. Experience with TNF inhibitors comes mainly from patients developing steroid-refractory severe colitis on ICI, particularly anti-CTLA4 [98, 99]. In those patients, TNF inhibitors are remarkably successful on immune-mediated colitis, particularly when initiated early after onset of colitis [99], and any deleterious effect regarding anti-tumour efficacy has not been reported [100, 101]. In mouse models of melanoma and colorectal cancer, blockade of TNF and IL-6 in the presence of anti-PD-1 even lead to a higher anti-tumour effect [102, 103]. Based on these observations and on the fact that excessive inflammation could be deleterious for the anti-tumour effect of ICI, some randomized clinical trials have begun associating ICI with anti-TNF or anti-IL-6 (e.g. NCT03293784, NCT03601611). On the other hand, in an *in vitro* study consisting of a co-culture with a colon cancer line and CD8 T cells treated with ICI, adjunction of anti-TNF to ICI decreased tumour cytotoxicity [104].

Another bDMARD, abatacept (a fusion protein of the extracellular domain of CTLA-4 and the Fc portion of IgG) has been demonstrated as effective in traditional entities such as rheumatoid arthritis or psoriatic arthritis; however, its mechanism of action of abatacept is the converse of that of ipilimumab, as it blocks the activating interaction between CD28 and CD80/86, rather than blocking the inhibitory interaction. Although there are no data evaluating the use of abatacept in rheumatic irAEs, its use is currently avoided in the treatment of irAEs based upon the mechanism of its action (and a hypothetical risk of interfering with the anti-tumour ICI action).

Finally, we note that in a case report, the use of secukinumab, an anti-IL-17 monoclonal antibody, in a patient with serious worsening of psoriasis and previous Crohn's disease led to recurrence of a metastatic colon cancer [105]. Thus, only randomized trials will reveal the safety of bDMARDs in this context.

Compared with non-cancer patients with undifferentiated arthritis, the proportion of patients receiving DMARDs seems to be rather low, which may be due to the preference of using glucocorticoids for irAEs in general and the prospect that a short course of glucocorticoids might be sufficient to overcome the irAE.

For myositis, in addition to moderately high doses of glucocorticoids, which seem effective regarding the myositis, severe manifestations such as bulbar symptoms may require intravenous immunoglobulin and plasma exchange. The frequent poor or even fatal outcomes, particularly of the latter, are probably due to the severity of these disease manifestations partially corresponding to the observations made in the non-cancer situation. However, not all cases of myositis might be due to ICI therapy. Instead, myositis, and particularly dermatomyositis (a well-known association) may be paraneoplastic, due to the underlying malignancy. This might also explain the high proportion of patients responding poorly or not responding to treatment. Although difficult to assess, further research is necessary to examine paraneoplastic *vs* ICI-induced aetiology.

Compared with the efficacy assessment of rheumatic irAEs treatments, the possible interference with an ICI-induced tumour response is even more complex. In this regard, a potential concern is that immunomodulatory/suppressive might dampen the anti-tumour immune response leading to worse cancer outcomes. Whereas in most of the published cases with immunomodulatory/suppressive treatment the tumour state was stable, in some cases the tumour progressed. Currently, there are not sufficient data within rheumatic irAEs to draw meaningful conclusions regarding an impairment of the ICI-induced anti-tumour response by an immunomodulatory/-suppressive treatment. However, data from patients with metastatic melanoma developing irAEs showed that immunomodulatory/-suppressive treatment had no impact on the tumour progression or overall survival [106]. Moreover, as indicated above, IrAEs occurring in patients with urothelial cancers treated with anti-PD1/PDL1 antibodies were associated with a better chance of anti-tumour response to ICI, even if the IrAE was treated with glucocorticoids [98]. We need further data, particularly for rheumatic and systemic irAEs to analyse the impact of immunomodulatory/-suppressive treatment on tumour progression.

Moreover, withdrawal is an important aspect in the management of rheumatic and systemic irAEs. In clinical trials and recommendations from the oncology field, ICIs may also be held or discontinued for severe symptoms, $\geqslant$ grade 3 by Common Terminology Criteria for Adverse Events grading [1]. According to this grading, most rheumatic irAEs would not be classified as $\geqslant$ 3. However, oncology and rheumatology grading systems for adverse events differ, and musculoskeletal events with substantial functional impact (e.g. limiting instrumental activities of daily living) may be only a grade 2 event by the Common Terminology Criteria for Adverse Events system used by oncology, whereas they would be a grade 3 event in the Rheumatology Common Toxicity Criteria system [57]. In rheumatology practice, ICIs would not only be withheld in case of severe manifestations such as life-threatening vasculitis or myositis but also in cases of severe other rheumatic irAE with great impact on the well-being of the patient. A practicable indicator for a necessity of withholding ICI treatment seems to be the need for (longer) use of high doses of glucocorticoids. ICI discontinuation was observed as highest in the myositis, vasculitis, lupus and scleroderma cases ($\sim$80%), followed by sarcoidosis (-like) ($\sim$65%), sicca syndrome ($\sim$60% and arthritis cases ($\sim$25%). Restarting ICI therapy can be considered when signs and symptoms are controlled; however, it should not be considered after occurrence of grade 4 (life-threatening) adverse events [20]. Whereas no systematic data are available for the recurrence of initial rheumatic irAEs after ICI re-treatment, recurrence of $\sim$ 25% (after resolution before) was observed for other irAEs after re-exposure [107, 108]. Given the vital importance for cancer patients and the possible better anti-tumour response in patients developing irAEs, the major goal should be the continuation of tumour immunotherapy. In this regard, rheumatologists should facilitate access for these patients for an early diagnosis of rheumatic irAEs and help oncologists to treat signs and symptoms to a tolerable level, which allows them to remain on their (effective) cancer treatment. Vice versa, oncologists should consult rheumatologists for an assessment with low threshold after the onset of rheumatic signs or symptoms in the context of CPI therapy and as soon as possible (ideally before initiating glucocorticoids and within days). Our proposal for the management of rheumatic/systemic irAEs according to entity and severity is summarized and shown in Table 2. Nevertheless, the choice to stop or to proceed with the ICI treatment should not only be based on the severity of rheumatic irAEs, the level of necessary immunosuppression, the cancer stage and ICI response, but also (if not most importantly) the shared decision with the patient.

Finally, it is important for the management of rheumatic irAEs that there is a continuous clinical follow-up monitoring irAE activity, efficacy of immunomodulatory/immunosuppressive treatment with the possibility to adapt treatment and withhold or restart the ICI treatment in close collaboration with the treating oncologist. Further research and clinical trials are needed to improve the treatment of rheumatic/systemic irAEs and understanding of the pathophysiology to optimize management.

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