Immune Checkpoint Inhibitor-induced Polymyalgia Rheumatica

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KEYWORDS

• Polymyalgia rheumatica • Immune-related adverse event • Mimics • Paraneoplastic • Disease model • Peresolimab • PD-1 agonist • PD-1 inhibitor

KEY POINTS

- Polymyalgia rheumatica (PMR) immune-related adverse events (ICI-PMR) are a distinct entity with many clinical, laboratory, and imaging similarities to classical PMR.
- ICI-PMR must be differentiated from other immune-related adverse events including inflammatory arthritis, as well as classical PMR mimics.
- Current ICI-PMR therapy is based on classical PMR treatment approaches, although immuno-oncological considerations must be incorporated through shared decision-making between patient and clinician.
- Comparisons between ICI-PMR and classical PMR are important as they may yield relevant implications for both, including the plausibility of therapeutic targets.

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Rheum Dis Clin N Am 50 (2024) 255–267
https://doi.org/10.1016/j.rdc.2024.02.001
rheumatic.theclinics.com

INTRODUCTION

Polymyalgia rheumatica (PMR) immune-related adverse events (ICI-PMR) are a subtype of rheumatic immune-related adverse event (irAE) arising following immune checkpoint inhibitor (ICI) immunotherapy. Contemporary ICI immunotherapy practice is dominated by inhibitors of the programmed death-ligand 1/programmed cell death protein 1 (PD-L1/PD-1) immune checkpoint, whose use only became widespread as recently as 10 years ago. Accordingly, the body of knowledge concerning irAEs remains in evolution. Despite occurring less frequently than inflammatory arthritis irAEs (ICI-IA),[1] the escalating use of ICI immunotherapy means recognition of ICI-PMR is increasingly important, in both clinical and research settings.

IMMUNE CHECKPOINT INHIBITOR'S FOUNDATIONS ON CURRENT CONCEPTS OF POLYMYALGIA RHEUMATICA

The concept of ICI-PMR is based on the disease PMR, which here we call "classical PMR" for clarity. Classical PMR tends to occur in older people with an average age of onset in the eighth decade. Its cause is unknown but immunosenescence and tissue aging are both likely to play a role.[2] Classical PMR is very rare under the age of 50 years. The clinical features of classical PMR include profound bilateral shoulder restriction, stiffness, and pain, arising from inflammation at musculotendinous structures of the shoulder and pelvic girdle, buttocks, and other tendinous insertions.[3] Elevation of acute phase markers is usual. PMR is frequently accompanied by constitutional symptoms such as fever, night sweats, weight loss, or depression. It tends to respond rapidly and completely to systemic glucocorticoid therapy in the form of 15 to 20 mg daily prednis(ol)one, which is then weaned over a prolonged period of some years. Relapse may occur during glucocorticoid wean, and this is treated by re-escalation of dose. More recently, conventional synthetic and biologic disease modifying antirheumatic drugs (csDMARD, bDMARD) have been used, reflected in the recent approval of interleukin (IL)-6 inhibition for the treatment of refractory or relapsing PMR.[4]

Management of patients diagnosed with classical PMR crosses organizational boundaries between primary care and rheumatology, and so much of the literature on classical PMR is based around describing heuristics and practices that have evolved over many years to ensure that patients are safely diagnosed and managed within this context.[5] The phenomenon of ICI-PMR brings new challenges of a third group of specialists—oncologists—who historically have had little experience of diagnosing classical PMR.[6] Therefore, it is worth mentioning some concepts that already exist in the classical PMR literature that might need to be re-evaluated in the trispeciality management of ICI-PMR.

MIMICS AND TRIGGERS OF CLASSICAL POLYMYALGIA RHEUMATICA

First, recognition of polymyalgic symptoms depends heavily on clinical experience. There has been concern historically as to whether this can be safely achieved in primary care.[7] The first concept to recognize is "PMR mimics." Historically, guidelines have focused on "safe and specific" diagnosis of classical PMR and ruling out various possible "PMR mimic" diseases. Cancer is one of the differential diagnoses considered where constitutional features are prominent. A comprehensive clinical evaluation may need to be supported by appropriate imaging tests (eg, contrast CT) to ensure mimics are considered. There are ongoing debates in rheumatology about

how broad the spectrum of classical PMR is—for example, whether elevated acute phase markers are required for a diagnosis, and if so what comprises the appropriate threshold.

The second concept to recognize is "PMR triggers." Various potential "triggers" of PMR have been reported including (occasionally) respiratory/viral infections or some vaccines[8]; causality is difficult to prove on an individual level, and it is debated whether this subset represents a distinct subset within classical PMR. If a patient presents with PMR-like features and is codiagnosed with cancer, then usually the cancer is addressed first, but sometimes the PMR symptoms persist despite treatment of the cancer. This is sometimes considered "paraneoplastic PMR"; there is little published research on this phenomenon.[9] If these ongoing PMR symptoms cause the patient functional limitation, the symptoms are usually pragmatically managed by the addition of low dose glucocorticoid therapy.

ICI-PMR, however, represents a novel clinical entity in that the presumed trigger is well defined and the pathogenesis appears highly plausible. The normal process of immunosenescence is accompanied by an increased expression of inhibitory checkpoint ligands, which serves to mitigate the clonal expansions that occur with aging; this underlies the common observation that clinical sequelae from varicella zoster virus reactivation (shingles) tends to occur in older people likely due to T-cell immunosenescence. In the context of cancer treatment, monoclonal antibodies against immune checkpoints (eg, PD-1, PD-L1) activate lymphocytes, increase lymphocytic infiltration into the tumor microenvironment, and augment the immunologic response to cancer. This ICI therapy is now a well-established part of the therapeutic armamentarium against many cancers. In the process of activating lymphocytes, however, autoimmune phenomena may arise, including some, like ICI-PMR, which closely resemble classical autoimmune diseases.

RESEMBLANCE OF IMMUNE CHECKPOINT INHIBITOR-INDUCED POLYMYALGIA RHEUMATICAL TO CLASSICAL POLYMYALGIA RHEUMATICA

Although ICI-PMR is considered a distinct clinical entity to classical PMR, patients with ICI-PMR typically experience a disease with striking clinical, laboratory, and imaging parallels to classical PMR. The profound bilateral shoulder restriction, stiffness, and pain of ICI-PMR, often accompanied by similar inflammatory changes at musculotendinous structures of the pelvic girdle, combined with constitutional symptoms, afflict and impair patients with ICI-PMR in a manner largely akin to patients with classical PMR. While some ICI-PMR may have a self-limiting, monophasic course persisting far shorter than classical PMR, most have a similar chronic course to classical PMR, which may persist even after ICI therapy is ceased. Previously, some presentations with aggressive peripheral synovitis discordant to other polymyalgic features were sometimes previously attributed to ICI-PMR but might now be labeled as ICI-IA.[10] Excluding such disconcordant presentations, most patients with ICI-PMR have clinical presentations that are currently difficult for clinicians to distinguish from classical PMR.

UNANSWERED QUESTIONS

Much still remains unknown about ICI-PMR. Not only do optimal definition, prognostication, and treatment remain uncertain, exactly how similar ICI-PMR is to classical PMR has not yet been determined. If these 2 phenomena are similar, however, it may prove advantageous to both entities, including utilizing classical PMR as a prototype for ICI-PMR and using ICI-PMR to understand therapeutic targets for classical PMR.

In this review, we consider the challenges in defining ICI-PMR, its clinical presentation and treatment, the difficulties patients and their clinicians face in making decisions about treatment of ICI-PMR, and how comparisons between ICI-PMR and classical PMR might proceed. We will exclusively consider de novo ICI-PMR irAEs, rather than ICI-associated relapse of PMR, since these are not necessarily the same mechanistically. ICI-related exacerbations of pre-existing autoimmune diseases will be addressed in "Pre-existing autoimmune diseases and immune checkpoint inhibitors for cancer treatment: Considerations about initiation, flares, immune-related adverse events, and cancer progression" by Jeffrey A. Sparks.

DEFINING POLYMYALGIA RHEUMATICA IMMUNE-RELATED ADVERSE EVENTS

It is important to establish a uniform definition of ICI-PMR for the research literature. It might not be sufficient to simply apply the current definition of classical PMR combined with an attribution to recent initiation of ICI therapy. Currently, the diagnosis of ICI-PMR is entirely reliant on clinical expertise developed in the context of classical PMR, but in the classical PMR, the risk–benefit balance of glucocorticoid therapy is judged in the light of a disease that does not in itself appear to shorten life. For ICI-PMR, these considerations are not the same, since every patient by definition has 2 diseases concurrently: cancer and ICI-PMR. Furthermore, there is a need to distinguish ICI-PMR from other irAEs.

Immune checkpoint inhibitor-induced polymyalgia rheumatica versus immune checkpoint inhibitor-induced inflammatory arthritis and other immune-related adverse events

Some difficulty exists in defining ICI-PMR, particularly in differentiating it from other rheumatic irAEs, such as ICI-IA. No investigation routinely undertaken in clinical practice has demonstrated the capacity to define ICI-PMR. Imaging or laboratory tests might, in isolation or combination, define ICI-PMR in the future. ICI-PMR demonstrates similar findings to classical PMR on PET–computed tomography (CT).[11,12] This imaging modality is often employed for cancer staging, and therefore, it may prove incidentally convenient for ICI-PMR diagnosis.[13] While PET/CT provides high specificity in classical PMR, its performance is yet to be tested in determining ICI-PMR among ICI-treated patients.

In fact, no approach has yet been elucidated fully, and robust clinical algorithms have similarly not been developed. In particular, no formal classification criteria currently exists for any rheumatic irAEs, although a development process sanctioned by the American College of Rheumatology (ACR) and the European Alliance of Associations of Rheumatology (EULAR) is currently being undertaken to develop such criteria for both ICI-PMR and ICI-IA.

From the start of this classification criteria initiative, it was thought necessary to consider these two irAEs synchronously. Such an approach was adopted primarily because while many patients present purely with features of either ICI-IA or ICI-PMR without any clinical suggestion of the other, some individuals do exhibit features of both presentations. For instance, some patients experience a rheumatic irAE initially presenting with symptoms characteristic of classical PMR, such as profound bilateral shoulder restriction and early morning stiffness, but subsequently develop persistent peripheral arthritis, often of large joints, as their most prominent feature, with few or no ongoing polymyalgic symptoms. Undoubtedly, this situation complicates accurate classification and would likely be dependent upon which stage of disease the assessment occurs.

Given that the persistent clinical manifestations affecting these patients become symptomatically indistinguishable from other patients with ICI-IA without a history of polymyalgic features, in the absence of validated classification criteria, their disease is most frequently attributed to ICI-IA (rather than ICI-PMR). While it is possible that their ICI-IA disease phenotype may possess some similarities to ICI-PMR, their ongoing investigation and management is less likely to do so and therefore will not be considered within the scope of this article.

Nevertheless, it has been observed that patients with ICI-PMR, similar to patients with classical PMR, might have peripheral joint involvement, including synovitis.[14] That said, the clinical presentation of ICI-PMR remains most notable for features other than peripheral joint involvement. When such peripheral involvement does occur in ICI-PMR, it is often, but not always, transient. Importantly, however, the presence of synovitis neither necessitates the diagnosis of ICI-IA nor excludes the diagnosis of ICI-PMR.

It should be noted that myositis irAEs (ICI-myositis) are often considered as a differential in those experiencing proximal myalgias. Just as classical idiopathic inflammatory myopathies differ from classical PMR, ICI-myositis differs from ICI-PMR in important but well-recognized ways. The presence of weakness independent of pain, and evidence of muscle inflammation and damage indicated by an elevation of muscle enzymes would point to ICI-myositis, with further evidence obtained from muscle histopathology, electromyography, myositis-specific autoantibodies, or imaging findings on MRI and/or PET/CT.[15]

Immune checkpoint inhibitor-induced polymyalgia rheumatica versus classical polymyalgia rheumatica

ICI-PMR can sometimes be clinically indistinguishable from classical PMR, given age-appropriate patients treated with ICI immunotherapy are at risk of incident classical PMR. It is notable that ICI-PMR has not been described in ICI immunotherapy-treated patients aged under 50 years, the age below which classical PMR rarely first develops. This does not necessarily mean that ICI immunotherapy does not cause ICI-PMR. Rather, the vast majority of patients receiving ICI immunotherapy are aged older than 50 years, and this predilection is likely relevant to both ICI-PMR and classical PMR.

It might be asked whether ICI-PMR is a real phenomenon at all or whether it is purely a coincidental diagnosis of 2 diseases concurrently (cancer and PMR) in individuals whose age puts them at greater risk of both. However, it does seem clear that ICI-PMR arises far more frequently in ICI-treated patients than would have been expected from the incidence of classical PMR in the general population of the same age group. This is reflected in pharmacovigilance studies that have observed disproportionate reporting of PMR associated with ICI therapy compared to other cancer therapies. Despite the likelihood of underdiagnosis by oncologists, cohort studies of ICI immunotherapy-treated patients have shown an incidence of ICI-PMR of up to 1% during the immunotherapy exposure period alone, substantially in excess of population estimates of less than 0.1%/y for classical PMR in age-appropriate populations.[16–18] It therefore stands to reason that ICI immunotherapy is associated with incident polymyalgic symptoms in substantially more people than could be attributed to classical PMR.

Given the background incidence of PMR in the population, there will always be a few patients who will coincidentally develop classical PMR during the period of their cancer treatment. As there is currently no reliable way to distinguish this phenomenon from ICI-PMR, at present by pragmatic application of "Occam's razor," patients developing a PMR-like illness during or shortly after ICI therapy would usually be considered

to have ICI-PMR. This recognition of the closely entwined scenarios of immune therapy and autoimmunity also facilitates combined multispeciality management and the future research that will be needed to inform shared decision-making for these patients.

Immune checkpoint inhibitor-induced polymyalgia rheumatica versus the "polymyalgia rheumatica mimics"

As alluded to above, standard practice in evaluating patients with suspected classical PMR is to exclude "PMR mimics" or non-PMR causes of arthralgia. In this context, setting aside the considerations of the various types of pain that might be related to local or systemic cancer treatments, common "PMR mimics" to consider include biomechanical and metastatic causes of arthralgia. Whether "paraneoplastic PMR" should be considered a PMR mimic, a PMR trigger or not PMR at all is currently an uncertain question that is not likely to be settled soon due to the comparative rarity of this phenomenon.

Biomechanical causes of arthralgia are common in older people, especially where there is physical deconditioning related to age, loss of muscle strength (sarcopenia), or changes in mobility. Rotator cuff tendinopathies, adhesive capsulitis, and osteoarthritis-related pain are all very common in older people and may worsen secondary to the physical and mental health impacts of cancer and its treatments, including ICI therapy.[19] Systemic glucocorticoids are not usual first-line treatments for biomechanical pain, with local therapies—including sometimes joint or soft tissue injections—being preferred. The expertise of rheumatologists can be of great value in providing a diagnosis and directing patients toward treatment options.[20]

Arthralgia in patients with a cancer diagnosis often raises concern for bony metastasis, which may cause anxiety for patients and clinicians alike. Concerns are raised where there is severe night pain or prominent constitutional symptoms such as night sweats. Investigations need to be pursued in close liaison with the relevant specialist teams.[21] The rheumatologist's role in rapidly differentiating inflammatory versus mechanical disease is highly useful to ensuring patient quality of life, optimizing tolerance of ICI immunotherapy, and reducing unnecessary glucocorticoid exposure.

Paraneoplastic syndromes may emerge at the time of ICI immunotherapy being commenced[22] and therefore may represent a relevant mimic of ICI-PMR. It is well established that classical PMR can occur as a paraneoplastic syndrome, independent of ICI immunotherapy exposure. This phenomenon of "paraneoplastic PMR" remains debated, with both its true nature and frequency uncertain.[9,23] In primary care datasets, malignancy is slightly more likely to be recorded during the 6 months following diagnosis of classical PMR; this is most frequently hematological malignancy such as lymphoma, perhaps reflecting the outcome of subsequent investigation of an anomalously elevated ESR that does not respond to glucocorticoid therapy as would be expected in classical PMR.[24] Given the difficulty of absolutely excluding "PMR mimics" in a primary care setting, it is questionable whether this really represents "paraneoplastic PMR," PMR mimic, or merely coincidental discovery of lymphoma due to the increased frequency of routine blood tests in the wake of a PMR diagnosis.

Historically, a recent diagnosis of cancer may have made a subsequent diagnosis of PMR less likely, due to the phenomenon of diagnostic overshadowing. This trend may be reversed with the recent recognition of ICI-PMR.

Relapsing seronegative symmetric synovitis with pitting edema (RS3PE) syndrome is another rheumatic disorder that has been identified as sometimes representing a paraneoplastic phenomenon.[25] It is commonly associated with polymyalgic features and is accepted as part of classical PMR's disease spectrum.[26–28] Furthermore, RS3PE has

been reported in the context of ICI immunotherapy and may represent an irAE.[29,30] Either as a paraneoplastic phenomenon or an irAE, it may require a different therapeutic approach to ICI-PMR,[31] with respect to glucocorticoid dosing and continuation of ICI immunotherapy. Consequently, it remains important to distinguish RS3PE from ICI-PMR, and we currently prefer to consider it as its own entity of ICI-RS3PE.

TREATMENT

As is the case for classical PMR, the mainstay of ICI-PMR therapy remains oral glucocorticoids, with the dose titrated according to polymyalgic symptoms.[32] Although early reports suggested a small number of patients might respond to nonsteroidal anti-inflammatory drugs (NSAIDs) alone, our experience is that, where persistent symptoms exist, such therapy is largely ineffective and does not replace the need to eventually treat with oral glucocorticoids. Furthermore, the potential toxicity of chronic NSAID therapy is not trivial within cancer survivorship cohorts, particularly relevant given favorable ICI response in patients with rheumatic irAEs.[33] While some ICI-PMR does appear to be monophasic, we have infrequently observed patients whose symptoms have spontaneously resolved in a satisfactory time frame without glucocorticoids. It is likely however that transient (undiagnosed) ICI-PMR may be more common than currently recognized; as for classical PMR, rheumatology practice is likely enriched for the subset that follows a more chronic or multiphasic course.

The necessary dose of oral glucocorticoid to initially manage ICI-PMR remains incompletely determined, but our experience is consistent with the literature in that prednisolone 10 mg daily consistently leads to incomplete symptomatic benefit. Prednisolone 15 mg daily leads to a complete resolution of symptoms in the majority of patients after 2 weeks of therapy, although some patients with atypical features may require higher doses.[10]

The ideal glucocorticoid tapering schedule has similarly not been established for ICI-PMR, and it should be noted that substantive variation in glucocorticoid weaning practice still exists for classical PMR, despite it being a more established disease entity.[34] The imperative to wean systemic glucocorticoids differs in ICI-PMR compared with classical PMR, given that glucocorticoid therapy may blunt ICI immunotherapy efficacy.[35] Conversely, there may be less concern about medium–long term glucocorticoid-related complications such as osteoporosis and the metabolic syndrome due to the individual's cancer-related prognosis.[36] In the authors' experience, an accelerated version of a classical PMR glucocorticoid wean can be trialed successfully in some patients but may prove insufficient in others.

Among patients with disease refractory to glucocorticoid weaning, it may be feasible to maintain glucocorticoid dosing at lower levels with a view to trialing a wean when ICI immunotherapy ceases. It is not clear whether this might be preferable to either conventional immunosuppressive (eg, methotrexate) or biologic treatments (eg, IL-6 inhibitors) in terms of ICI immunotherapy efficacy.[37] Some patients, given their need for ongoing ICI immunotherapy and high-dose glucocorticoids, may be candidates for biologic treatments. IL-6 R inhibitors have been trialled in other rheumatic irAEs, and while their effect on tumor response remains incompletely determined, IL-6 R inhibitors are likely preferable to glucocorticoids.[38] More recently, IL-6R inhibitors (both sarilumab and tocilizumab) have been investigated in classical PMR and have shown efficacy both in relapsing/refractory disease and for new diagnoses.[4,39,40]

A fundamental but often neglected aspect of managing classical PMR in rheumatology practice is the management of concomitant arthralgias of biomechanical origin, which can

often complicate the weaning course of glucocorticoid therapy due to the impact of chronic glucocorticoid therapy on body composition, ability to rebuild muscle strength and indirect impacts via exacerbation of other physical and mental health conditions. Chronic glucocorticoid therapy may also cause iatrogenic adrenal insufficiency, which can make it difficult to stop systemic glucocorticoids without a very prolonged wean.[41]

Often, discontinuation of ICI immunotherapy may be considered by oncology clinicians in managing ICI-PMR. In our opinion, ICI-PMR is highly likely to be able to be managed without ICI immunotherapy discontinuation, but if the benefit from ongoing ICI immunotherapy continuation is already considered to be marginal (either due to futility or due to a sustained good response), then discontinuation may be considered on a risk–benefit basis. Critical to this decision is an understanding of the impact on both the ICI-PMR and underlying malignancy.

The decision here perhaps depends on whether the ICI is considered as a "trigger" or as a "driver" of ICI-PMR. Further research on the outcome of ICI cessation in these patients is needed.

SHARED DECISION-MAKING BETWEEN PATIENT AND CLINICIAN

The needs of the patient in ICI-PMR differ from both classical PMR and ICI-IA. Patients with all rheumatic irAEs must navigate a tension between competing clinical interests in managing their irAE and their cancer.[36] Their cancer may be life-limiting, particularly in the medium term, and managing this is probably but not definitively improved by continuation of ICI immunotherapy and minimization of systemic glucocorticoids. Their rheumatic irAE may not be life-limiting but may severely impact their short-term quality of life over what, in some, will inevitably be a limited life span. This irAE will very likely be improved in the short-term by discontinuation of ICI immunotherapy and the sustained use of systemic glucocorticoids.

This balance is difficult in ICI-PMR. Systemic glucocorticoids are the only established therapy, and they may be needed for a sustained period, albeit at lower doses. Patients may be conflicted about the speed of glucocorticoid weaning. To compound matters, treating oncologists may be unfamiliar with prednisolone dosing relevant to ICI-PMR, which can differ substantially from other irAEs and nonrheumatic irAEs such as ICI-colitis or ICI-pneumonitis, which necessitate much higher doses. Finally, rheumatologists might instinctively consider conventional glucocorticoid toxicity, which may be relevant for patients who enter survivorship but may also add an additional medical burden for those who do not.

Primarily, the needs and desires of patients must be articulated and considered. Each patient must make decisions with appropriate clinical guidance about balancing short-term symptoms and quality of life against medium-term survival. These choices must be dynamic over the time that the irAE requires management but are likely to be influenced by personal priorities and experience. Such decision-making is strengthened when informed by collaborative assessment and communication between oncologists and rheumatologists. A clear outline early on in the course of ICI-PMR management assists patients in navigating this balance. Patient education is necessary as ICI-PMR does not necessarily fit the popular concept of "treatment side-effect" but might be better viewed as a newly triggered autoimmune disease that requires comanagement across multiple specialities and services.

FUTURE PROSPECTS

Both ICI-PMR and classical PMR have disease aspects that remain inadequately understood, but the broad similarities between the two may provide the opportunity for

bidirectional insights, which might improve clinical care and research for both. While they currently are considered to be distinct disease entities, comparisons between the two may yield important insights into both.

ICI-PMR is a young disease with a greenfields understanding of its pathology. These questions cannot be answered without a consistent definition of what ICI-PMR is for the purposes of research studies (classification criteria), its natural history with and without specific treatment, and its response to ICI withdrawal. Classical PMR, in comparison, has had many of these elements established, albeit in a very different and arguably more straightforward clinical context. ICI-PMR is an example of the difficulties of managing multiple long-term conditions where the causes and treatments of those conditions are closely intertwined and causality may be difficult to unravel in individual patients.

Patients with ICI-PMR need research and treatment now, and for the time being, it is pragmatic to apply the concepts and tools that have been developed for classical PMR. However, as time goes on, it is possible that these concepts and tools may either converge, if ICI comes to be considered as just one possible "trigger" of classical PMR, or diverge, due to the defined context of ICI-PMR. For example, if ICI therapy contributes to "driving" ICI-PMR then this could have important implications for the treatment of ICI-PMR and of the cancer itself.

Classical PMR remains poorly understood and very little is known about what causes it. There appears to be a persistent activation of circulating myeloid cells preceding disease that persists despite therapy.[42] The cause of this myeloid activation is unknown. Most of the pathophysiological research of potential relevance of PMR has been conducted in the vasculitis, giant cell arteritis (GCA), which is considered to be a related but distinct disease.[2] Intriguingly, in GCA, vascular dendritic cells have defective expression of PD-L1 allowing a break in tolerance that promotes ingress of autoreactive T-cells into the vascular wall.[43,44] Despite this, it is very rare for GCA to occur as an irAE suggesting that at least for GCA, an immune-checkpoint defect is not sufficient to induce disease.

As with many inflammatory rheumatic diseases, patients with PMR tend to present to medical care only when the disease is well established, by which time any clues as to the pathophysiological events associated with the initiating break in self-tolerance may have been "overwritten" by the intensity of the systemic inflammatory response once the inflammatory phase has become established. Identifying patients in the prodromal phase of PMR has historically been virtually impossible. ICI might recapitulate part of the earliest initiating events of classical PMR. Thus, ICI-PMR might be considered as a human model of induced disease for classical PMR that may allow study of the way the disease evolves in the lead-up to clinical presentation with ICI-PMR, as well as a better understanding of which patients receiving ICI are more susceptible to ICI-PMR than others who do not develop irAE or who develop other irAEs.[45] These insights might generate new hypotheses that could be translated across to classical PMR.

Clinical observations of disease in humans can derive so-called bedside-to-bench insights into pathophysiology[46] and, as in the case of romosozumab for osteoporosis, lead to successful therapeutic development.[47] Bedside-to-bench insights relevant to ICI-PMR raise questions about the therapeutic targeting of PD-1 in the treatment of classical PMR, especially given its seeming importance in the development of de novo disease. A PD-1 agonist, peresolimab, is currently under development for use in rheumatoid arthritis, with promising outcomes reported in patients whose disease is refractory to other therapies,[48] and other PD-1 agonists are in earlier stages of development. It stands to reason that PD-1 agonists might have a role in classical PMR therapy, particularly earlier in disease where no approved therapies exist.

In order for these comparisons to be definitely relevant, these similarities need to be demonstrated over multiple domains. When an animal model is being validated, considerations are made of measurement properties including face validity, predictive validity, and target construct validity.[49] While such validation must be modified to be relevant to the purpose of the model, this presents a relevant framework for comparisons between ICI-PMR and classical PMR. To be a valid comparator, a subset of ICI-PMR would ideally maintain face validity with similar, specific clinical manifestations to classical PMR (from symptomatic descriptions and severity, laboratory test changes, and imaging findings), predictive validity with a similar response to therapy (particularly to glucocorticoids), and target construct validity by evoking similar immunologic changes. If a persistent deficiency in immune checkpoint function plays a role in perpetuation of classical PMR, then it stands to reason that PD-1 agonists might be worth investigating as a potential treatment strategy for classical PMR, depending on whether immune checkpoints might play a role in triggering PMR, driving classical PMR, or both.

SUMMARY

As a newly emerging disease, which is becoming more common with the increasing use of ICI immunotherapy, ICI-PMR requires significant effort to improve its management, including its optimal treatment. Disease definition will help facilitate both research and clinical practice in ICI-PMR, but in-depth comparisons between ICI-PMR and classical PMR also have the potential to accelerate advancement in both ICI-PMR and classical PMR. Ultimately, this has the potential to assist clinicians and their patients making difficult decisions in both diseases.

CLINICS CARE POINTS

- Based on our current understanding, ICI-PMR diagnosis can be undertaken with many of the same approaches as classical PMR.
- While glucocorticoids may be dosed similarly in ICI-PMR as in classical PMR, some patients may respond to an abbreviated tapering schedule.
- Treatment approaches should be tailored to individual patients through shared decision-making, based on their underlying cancer, ICI treatment intent, irAE impact and treatment response, and personal preferences.

DISCLOSURE

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the study described in this article. D.F.L. Liew and R.R.C. Buchanan declare no relevant interests. C.E. Owen declares: consultancy and advisory board participation for Abbvie; speaking honoraria from Abbvie, Janssen, Novartis, and Roche. A. Tison declares consulting fees from Galapagos, speakers bureaus from Bristol-Myers Squibb, congress fees: Sanofi and Abbvie. S.L. Mackie reports: Consultancy on behalf of her institution for Roche/Chugai, Sanofi, AbbVie, AstraZeneca, and Pfizer; Investigator on clinical trials for Sanofi, GSK, and Sparrow; speaking/lecturing on behalf of her institution for Roche/Chugai, Vifor, Pfizer, UCB, Novartis, and AbbVie; chief investigator on STERLING-PMR trial, funded by the National Institute for Health and Care Research (NIHR); patron of the charity PMRGCAuk. No personal remuneration was received for any of the above activities. Support from Roche/Chugai to attend EULAR2019 in person and from Pfizer to attend ACR

Convergence 2021 virtually. S.L. Mackie is supported in part by the NIHR Leeds Biomedical Research Center. The views expressed in this article are those of the authors and not necessarily those of the NIHR, the NIHR Leeds Biomedical Research Center, the National Health Service or the UK Department of Health and Social Care. M. Yates reports advisory board fees for BioGen. S.E. Sattui is by the Bristol Myers Squibb Foundation Robert A. Winn Diversity in Clinical Trials Career Development Award. S.E. Sattui has received research funding from AstraZeneca and GlaxoSmithKline (clinical trials) and participated in consulting and advisory boards for Sanofi and Amgen (funds toward research support). S.E. Sattui has received speaker fees from Fresenius Kabi (funds toward research support). D.F.L. Liew conceptualized the article, and wrote the original draft. All authors were responsible for drafting, reviewing, and editing the final article.

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