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EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors

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Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-217139).

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Received 10 February 2020
Revised 3 April 2020
Accepted 7 April 2020
Published Online First 23 April 2020

To cite: Kostine M, Finckh A, Bingham 3rd CO, *et al*. *Ann Rheum Dis* 2021;**80**:36–48.

ABSTRACT

Background Rheumatic and musculoskeletal immune-related adverse events (irAEs) are observed in about 10% of patients with cancer receiving checkpoint inhibitors (CPIs). Given the recent emergence of these events and the lack of guidance for rheumatologists addressing them, a European League Against Rheumatism task force was convened to harmonise expert opinion regarding their identification and management.

Methods First, the group formulated research questions for a systematic literature review. Then, based on literature and using a consensus procedure, 4 overarching principles and 10 points to consider were developed.

Results The overarching principles defined the role of rheumatologists in the management of irAEs, highlighting the shared decision-making process between patients, oncologists and rheumatologists. The points to consider inform rheumatologists on the wide spectrum of musculoskeletal irAEs, not fulfilling usual classification criteria of rheumatic diseases, and their differential diagnoses. Early referral and facilitated access to rheumatologist are recommended, to document the target organ inflammation. Regarding therapeutic, three treatment escalations were defined: (1) local/systemic glucocorticoids if symptoms are not controlled by symptomatic treatment, then tapered to the lowest efficient dose, (2) conventional synthetic disease-modifying antirheumatic drugs, in case of inadequate response to glucocorticoids or for steroid sparing and (3) biological disease-modifying antirheumatic drugs, for severe or refractory irAEs. A warning has been made on severe myositis, a life-threatening situation, requiring high dose of glucocorticoids and close monitoring. For patients with pre-existing rheumatic disease, baseline immunosuppressive regimen should be kept at the lowest efficient dose before starting immunotherapies.

Conclusion These statements provide guidance on diagnosis and management of rheumatic irAEs and aim to support future international collaborations.

INTRODUCTION

Although the concept of immunotherapy in cancer is far from new, monoclonal antibodies targeting immunological checkpoints or 'checkpoint inhibitors' (CPIs) represent a growing class of agents across multiple tumour types and at all stages of disease. Agents targeting the T-cell cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death-(ligand) 1 (PD-1/PD-L1) coinhibitory receptors marked a turning point in the success of immunotherapeutic approaches.[1–3] By enhancing antitumour T-cell activity, unprecedented long-lasting tumour responses were observed in patients with unresectable or advanced metastatic disease.[4–7] The clinical value of these immune CPIs, as single agents or in combination, is being investigated in various solid tumours and haematological malignancies, and their use is expanding rapidly.[8] So far, the Food and Drug Administration and the European Medicines Agency approved seven immune checkpoint-blocking antibodies in selected cancers: one anti-CTLA-4 (ipilimumab), three anti-PD-1 (nivolumab, pembrolizumab and cemiplimab) and three anti-PD-L1 (atezolizumab, avelumab and durvalumab).

The T-cell activation induced by CPIs commonly promotes inflammatory or autoimmune-like side effects, known as immune-related adverse events (irAEs).[9] Compared with conventional cancer therapies, this spectrum of toxicities is unique and can affect any organ system, most frequently the skin, gastrointestinal tract, endocrine glands and lung. Among irAEs, specific rheumatic manifestations have been described rather rarely in randomised clinical trials, but are much more common in clinical practice. The clinical features of rheumatic irAEs have been described in a growing number of case series and reports.[10] However, despite the growing interest for irAEs among rheumatologists, evidence is lacking for the optimal diagnostic approach and the management of these patients in ways that also permit effective antitumour therapy to continue. According to a recent survey, a large proportion of

rheumatologists have limited experience and little confidence in managing rheumatic irAEs, highlighting the need for education and recommendations in this emerging condition.[11]

In 2017, the European Society for Medical Oncology developed clinical guidelines for the management of immune toxicities and mentioned the paucity of literature on management of rheumatic irAEs.[12] Three other consensus recommendations have been proposed by the Society for Immunotherapy of Cancer, the American Society of Clinical Oncology and The National Comprehensive Cancer Network, which among others included the management of inflammatory arthritis, polymyalgia rheumatica and myositis.[13–15] This European League Against Rheumatism initiative assembled international experts primarily from the rheumatology and immunology but also the oncology field with the explicit goal of generating the first set of recommendations for the diagnosis and the management of rheumatic irAEs arising as a direct consequence of CPI. Rheumatologists, but also in some countries internists and immunologists, have to play a pivotal role in developing with the oncologists a patient-centred approach to improve the management of rheumatic irAEs. While the initiative primarily set out to guide clinicians, it is noteworthy that there is limited and rapidly changing literature and that future additional studies can drastically change the profile for diagnosis and management. This area will be a continually evolving field; therefore, the accompanying comments may also serve as a framework for future longitudinal cohorts and/or clinical studies.

METHODS

After approval by the European League Against Rheumatism Executive Committee, an international task force was convened to develop points to consider for the diagnosis and the management of rheumatic irAEs due to cancer immunotherapy. Among these members, were 19 clinical experts from Europe and North America (14 rheumatologists including 2 delegates of the European League Against Rheumatism young rheumatologists' network EMEUNET, 2 internists and 3 oncologists), 1 clinical epidemiologist, 1 allied health professional and 2 patient representatives from the PARE network of patient research partners. The process adhered to the updated European League Against Rheumatism standardised operating procedures for the development of recommendations.[16]

In July 2018, the first meeting was convened in Zürich, Switzerland, to define the focus of the task force, identify the target population and the research questions for the systematic literature review (SLR). The SLR was performed by the research fellow (MK), with support from the clinical epidemiologist (AF) and a librarian (Catherine Weill), to identify relevant publications through December 2018. Based on the findings of the SLR, a first draft of points to consider including 12 items was prepared by the fellow (MK) and the two convenors (TS and XM).

SLR results were presented at a second meeting that was held in Zürich, Switzerland, in January 2019. Following the evaluation of literature and a group discussion of the first draft of propositions, the task force formulated overarching principles and consensus statements. Each proposal was then submitted to a voting process, requiring at least 75% of votes in the first ballot for each recommendation to be accepted. In case this threshold was not achieved, further discussion and textual changes were proposed for a second round, for which a 67% majority was required. Five members of the task force could not attend this second meeting, but they subsequently commented and voted on each statement by email. The level of evidence (LoE) and grade of recommendation was based on the Oxford Levels of Evidence.[17] After this second face-to-face meeting, members of the task force were asked to anonymously rate each item in an online survey, on a scale of 0 (absolutely disagree) to 10 (absolutely agree) to assess the level of agreement (LoA). Furthermore, the task force agreed on adding relevant references published between the SLR and the writing of this manuscript. The manuscript was reviewed and approved by all task force members and the European League Against Rheumatism Executive Committee before submission.

RESULTS

Systematic literature review

The literature search strategy and summary of results are detailed in online supplementary data. The first objective was to identify phase III clinical trials to assess the frequency and type of rheumatic and musculoskeletal diseases' (RMDs) complaints associated with CPI compared with the comparator group. The search was performed using Medline, Embase and the Cochrane Library, through December 2018. Among 630 references identified, 22 studies were selected for inclusion. The second objective was to obtain detailed information on rheumatic and musculoskeletal symptoms that have been described under CPI treatment. The third objective was to assess outcomes in patients with pre-existing autoimmune diseases. Therefore, relevant keywords relative to three key domains were used in Medline and Embase databases: immune CPIs, rheumatic and systemic diseases and adverse events. Abstracts from the last two European League Against Rheumatism and American College of Radiology meetings were included, combined with manual searches from references of the selected articles. From among 2156 references identified, 170 were included, including pharmacovigilance registries (n=5), case series (n=51) and case reports (n=114).

After group discussion of the results of the SLR, the consensus process was initiated and the full task force agreed on a final set of 4 overarching principles and 10 points to consider (table 1).

Overarching principles

A. Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors (LoE na; LoA 9.6).

Analysis of phase III clinical trials revealed that arthralgia, arthritis, myalgia, myositis, dry mouth, musculoskeletal and back pain were reported in patients receiving CPI. However, their frequency was not significantly different to that of patients receiving chemotherapy or placebo.[5 18–38] Data from several series, both retrospective and prospective, reporting prevalences of rheumatic irAEs in real life, ranging from 1.5% to 22%, suggest that rheumatic irAEs are under-reported in clinical trials.[39–54] Of note, an heterogeneous definition of rheumatic irAEs may explain such wide interval. Many clinical trials do not report rheumatic irAEs (by disregarding of musculoskeletal/rheumatic events as a distinct organ system, even in the online supplementary data) or partially only report high-grade and/or frequent adverse events (ie, occurring in ≥10% of the patients). Therefore, the task force wanted to emphasise with this first principle that rheumatic and musculoskeletal manifestations are a relevant part of the broad spectrum of irAEs.

B. Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists (LoE na; LoA 9.5).

Table 1 Overarching principles and points to consider for the diagnosis and management of rheumatic irAEs

		LoE	GoR	LoA (0–10) mean (SD)
Overarching principles				
A.	Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors.	n.a.	n.a.	9.6 (0.7)
B.	Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists.	n.a.	n.a.	9.5 (1.1)
C.	Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms.	n.a.	n.a.	9.1 (1.2)
D.	The role of rheumatologists is to assist oncologists in differential diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy.	n.a.	n.a.	9.5 (0.9)
Points to consider				
1.	Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs.	4	C	9.5 (1.2)
2.	Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients.	5	D	9.4 (1.3)
3.	Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy.	4	C	9.5 (0.9)
4.	In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms.	4	C	9.4 (1)
5.	csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing.	4	C	9 (1.2)
6.	For patients experiencing severe immune-related rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis.	4	C	8.8 (1.2)
7.	The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient.	5	D	9.4 (1)
8.	Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary.	4	C	8.9 (1.2)
9.	A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs.	4	C	9 (1.3)
10.	Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatological assessment should be performed.	5	D	9 (1.3)

GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level.
LoE: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-6, interleukin 6; irAEs, immune-related adverse events; IVIg, intravenous immunoglobulin; LoA, level of agreement; LoE, level of evidence; RCT, randomised clinical trial; RMD, rheumatic and musculoskeletal disease; TNF, tumour necrosis factor.

Rheumatic and musculoskeletal irAEs occur in a context of cancer; therefore, a dialogue between rheumatologists and oncologists is important to balance the harm and risk of oncology treatment and immunosuppressive drugs. The most important stakeholder is the patient. Shared decision between a patient and his/her rheumatologist is a fundamental principle of RMDs management, as illustrated by its representation as an overarching principle in several European League Against Rheumatism recommendations.[55–57] Because evidence-based data for irAEs management are limited, and irAEs can have a large impact on the quality of life, patient's preferences and discussions concerning risks and benefits of each treatment option are even more important.

C. Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms (LoE na; LoA 9.1).

IrAEs may affect any organ system including the rheumatic and musculoskeletal system. Some patients may even experience multiple organ toxicities in sequence or concurrently. The importance of developing a local multidisciplinary network of oncologists and specialists of all organ system potentially involved in the management of irAEs has been recently highlighted.[58 59] Rheumatologists should actively engage in these local multidisciplinary networks as valuable members due to their knowledge of clinical immunology, their expertise in multiorgan autoimmune disease and their long-standing

experience with the use of immunosuppressive drugs and biological therapies.[60] This engagement should also include efforts aimed at improving patient education before or when starting cancer immunotherapy, to prevent delay in diagnosis when rheumatic or musculoskeletal side effects occur. Patients have reported that they were informed about other immune-related side effects more than rheumatic or musculoskeletal symptoms.[61] Furthermore, since the rheumatic and the cancer disease both induce high impact on the patient's life, even when independently considered and when disease activity is controlled (ie, fatigue, pain, functional impairments, emotional problems, secondary effects of the treatments), the value of an interdisciplinary collaboration between the rheumatologist and the oncologist is worthwhile.

D. The role of rheumatologists is to assist oncologists in establishing the diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy (LoE na; LoA 9.5).

This principle aimed to better define the role of rheumatologists as oncologists' partners based on the clinical experience of the task force members. Once a patient with cancer receiving immunotherapy is referred for evaluation of rheumatic or musculoskeletal symptoms, the rheumatologist should consider several potential aetiologies: tumour progression, paraneoplastic syndromes, non-rheumatic events (ie, viral infection, thrombosis, endocrine abnormality), all already considered by the referring oncologist, or rheumatic/systemic irAE or immune non-related adverse events. This aspect of differential diagnosis is also described in more detail in recommendation 3. Once a rheumatic irAE is diagnosed, the supervising rheumatologist should propose an appropriate treatment to relieve patient's symptoms to an acceptable level with the objective of maintaining quality of life and permitting continuation of effective cancer immunotherapy, if this is recommended by the oncologist. This treatment goal is different to classic rheumatic entities, in which usually remission is the targeted treatment outcome.

Points to consider

1. Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs (LoE 4; LoA 9.5).

While arthralgia and myalgia were the most commonly reported rheumatic irAEs in clinical trials, numerous case series and reports have captured a broader spectrum of de novo rheumatic and systemic manifestations that can occur with cancer immunotherapy.[62–64] Polymyalgia rheumatica (PMR)-like syndromes and inflammatory arthritis syndromes are two of the major clinical presentations encountered.[39–41 48 65 66] PMR-like manifestation occurred with a median exposure time to CPI of 60 days, but also much later (IQR 24–210 days). Exposure time to CPI was generally longer for patients experiencing inflammatory arthritis (median 120 days, IQR 48–262 days). In addition, a variety of other rheumatic syndromes have been reported. These include arthralgia; monoarthritis, oligoarthritis or polyarthritis; reactive arthritis; psoriatic arthritis (PsA); remitting seronegative symmetrical synovitis with pitting oedema (RS3PE); tenosynovitis; enthesitis; non-inflammatory musculoskeletal conditions and osteoarthritis.[41 44 46 51 66–77] Importantly, autoantibodies are often absent. In arthritis, only a few patients are positive for rheumatoid factor (RF; n=20, range 18–246 UI/mL) and/or anti-citrullinated peptide antibodies (ACPAs; n=14, range 18–614 U/mL).[78] Instead, positivity of antinuclear antibodies (ANAs) is observed, but often at a low titre (range 1:80 to 1:3200, one patient with ANA 1:12 800 and only 35 patients with ANA >1:160). Similarly, acute phase reactants may be normal in some patients with PMR-like presentations.[41] Overall, around 20% of patients fulfilled classification criteria of rheumatoid arthritis (RA) (55/271) or PMR (11/52). This percentage was higher (55%) for PsA (6/11), as well as in a recent series of PMR-like syndrome (37/49; 75%).[79] The first observation of recurrent pseudogout flares 7 to 10 days after each nivolumab infusion has been recently reported.[80]

Several cases of myositis have been reported, with frequent limb-girdle myalgia and weakness that may mimic a PMR-like condition.[81–83] Because it represents a potentially life-threatening complication, the task force decided to formulate a dedicated recommendation on myositis (*recommendation 8*).

Among systemic manifestations, sicca syndrome has been described early on, presenting mainly with dry mouth, and possible associated neurological symptoms in a few patients.[40 48 65 66 84–87] Two major studies on CPI-induced sicca syndrome were published in 2019 and therefore included in this manuscript. The ImmunoCancer International Registry reported on 26 patients experiencing CPI-associated sicca syndrome. This mainly included men, with frequent organ-specific autoimmune manifestations but lower prevalence of autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) in comparison with classical Sjögren's syndrome.[88] Interestingly, a predominant T-cell infiltrate with acinar destruction has been reported in salivary glands, distinct from the histological profile of idiopathic primary Sjögren's syndrome. Authors hypothesise that CPI therapy may break immune tolerance locally leading to the activation of cytotoxic T cells damaging the salivary epithelium.[89]

Other systemic manifestations have been described, including sarcoidosis or sarcoid-like reactions.[90–93] The diagnosis is usually suspected through imaging when new hilar lymphadenopathy or pulmonary nodules are detected in imaging, requiring biopsy. Half of patients experienced cutaneous manifestations (nodules, rash), and some patients had cough/dyspnoea (29%) and arthralgia/arthritis (18%). Uveitis, parotitis, hypercalcaemia and neurological symptoms are rarely reported. Some patients experienced systemic sclerosis or scleroderma-like reactions, all presenting with skin thickening, but only one with new-onset Raynaud's phenomenon.[48 94–96] None tested positive for specific autoantibodies. Since PD-1-deficient mice spontaneously developed lupus-like autoimmune diseases with arthritis and glomerulonephritis, such clinical phenotypes could be expected in patients treated with anti PD-(L)1 agents, but are not observed. A few cases of lupus-like cutaneous reaction and one Jaccoud arthropathy have yet been reported with anti-PD-1 agents, and only one lupus-like nephritis was attributed to anti-CTLA-4 treatment.[97–102]

All vessel-sized vasculitis (eg, large, medium and small vessels) with various clinical manifestations, including purpura, digital necrosis arthralgia, arthritis, myalgia, fever, fatigue and abdominal pain have also been reported.[40 48 84 103–113] Of note, ANA, antineutrophil cytoplasmic antibodies (ANCAs), cryoglobulin and RF were rarely positive. Analysis of the WHO pharmacovigilance database revealed that temporal arteritis (n=16) was particularly over-reported with ipilimumab monotherapy treatment.[114] The first case of granulomatosis with polyangiitis with a high anti-PR3 ANCA titre was reported in 2019.[115]

Recently, patients experiencing rapid bone loss with CPI leading to multiple fractures were reported, raising the question of a potential influence of immune activation on bone metabolism.[116]

Importantly, rheumatic and/or systemic irAEs may occur across all classes of CPI, most frequently and severely with combination treatments and may be associated with other organ-specific irAEs.

2. Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients (LoE 5; LoA 9.4).

The data that are available regarding the process of referral to a rheumatologist suggests that this is not widely done and might lead to delay in diagnosis. In one series, only 4 out of 12 patients experiencing rheumatic irAEs were reviewed by rheumatologists.[43] One cohort reported an average of 9.5±9.3 days between the counselling request and the first rheumatologist visit and 2.5±4.4 months from the start of arthralgias to the confirmation of synovitis.[67] Two other series reported a median of 34 days (range 16–210 days) and 7 days (range 1–57 days) before a rheumatology appointment.[66 117] Rheumatic side effects of CPI appear underappreciated, which probably delays proper assessment and treatment. However, as mentioned in the overarching principles, a prompt rheumatological evaluation should support rapid shared treatment decision to relieve patient symptoms, maintain a good quality of life and allow pursuing an effective cancer immunotherapy.

Currently, algorithms for irAEs management are based on the severity/grade of the irAE according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The first international guidelines recommended referral to a rheumatologist in the case of severe symptoms not responding to glucocorticoids (grade 3). Subsequently, prompt referral was proposed as soon as the patient experienced moderate pain associated with signs of inflammation (grade 2).[12–14] While CTCAE grading is routine for oncologists, and a requirement for clinical trials, rheumatologists are less familiar with this grading which do not accurately reflect the spectrum or severity of rheumatic or systemic manifestations (online supplementary table S1). Accordingly, the task force decided not to use the CTCAE grading system to prioritise referral but instead to recommend prompt assessment, ideally before starting glucocorticoids. For this purpose, rheumatologists should be encouraged to offer facilitated access since they may be able to avoid systemic glucocorticoids or use lower dose than oncologists to manage rheumatic toxicities.

3. Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy (LoE 4; LoA 9.5).

The first part of this statement has previously highlighted the overarching principle of defining the role of the rheumatologist (*overarching principle D*). While delaying the diagnosis of irAEs and its adequate treatment may result in a worse prognosis regarding both CPI adherence and immune-mediated tissue/organ destruction, focusing only on irAEs without considering other differential diagnoses may also be inappropriate. CPIs are commonly administered to patients with advanced cancer, and so new rheumatic/musculoskeletal symptoms must raise suspicion of cancer progression, as well as the lack of improvement of inflammatory arthritis with glucocorticoids (ie, possibility of metastases or paraneoplastic syndrome).[118 119] Advanced imaging, such as CT scan, MRI, bone scintigraphy or positron emission tomography-CT, may be helpful in arriving at such a diagnosis. The diagnosis of irAEs versus metastasis may become even more challenging as non-malignant resorptive lesions have recently been described, which can mimic metastases.[116] Pulmonary sarcoidosis-like lesions may also be first considered as tumour progression.

Immunological toxicities may also manifest as paraneoplastic syndromes. Current literature covers mainly paraneoplastic neurological syndromes with few published data regarding paraneoplastic rheumatic syndromes.[120 121] However, based on the clinical experience of task force members, the group agreed to include paraneoplastic syndromes in the differential diagnosis of rheumatic irAEs to inform clinicians that they may encounter newly and not pre-existing paraneoplastic syndromes following CPI therapy, notably hypertrophic osteoarthropathy. RS3PE and dermatomyositis were also reported, either as paraneoplastic syndromes or induced by CPI therapy, but one may not be able to make the distinction when appearing under CPI therapy.

The term ‘unrelated rheumatic diseases’ covers manifestations for which the causal link with cancer immunotherapy is not obvious, such as shoulder tendinitis, lateral epicondylitis, non-inflammatory back pain or complex regional pain syndrome. The task force agrees that it may be difficult to establish when a specific rheumatic feature can be considered related or unrelated to the administration of CPI. Using the adverse drug reaction probability score (Naranjo scale) may help to assess the causal link with CPI therapy.

The task force proposes that the key objective of the diagnostic work-up is to document evidence of target organ inflammation. By adopting the term target organ inflammation, the task force wants to emphasise that priority for the supervising rheumatologist is not only to search for joint inflammation but also to document evidence of any organ inflammation according to the symptoms presented (muscle, fascia, vessels, heart, lung, skin, endocrine glands, salivary glands, etc), either clinically or preferably by using appropriate laboratory tests, imaging and tissue biopsy.

Tissue diagnosis should be decided on a case-by-case basis, based on the type and severity of rheumatic irAE, when other supportive information would not be sufficient to make a clinical decision in terms of therapy. Notably, histopathological data may be frequently indicated in patients presenting with vasculitis, sarcoidosis and myositis, but should not interfere with starting treatment, particularly with myositis or patients presenting with life-threatening irAE. On the other hand, synovial biopsies will not change the acute management of inflammatory arthritis. They may provide insights into targeted therapies with glucocorticoid saving approaches, but are not recommended for daily practice.

4. In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms (LoE 4; LoA 9.4).

In the absence of contraindications, symptomatic treatment including non-steroidal anti-inflammatory drugs and/or analgesics should be the initial treatment for mild-to-moderate rheumatic manifestations. There are no data on the efficacy of symptomatic therapies in the context of systemic manifestations. An anti-inflammatory effect of these drugs can be expected within several hours or a few days. Additionally, intra-articular glucocorticoids should be considered in the context of monoarthritis

or oligoarthritis, combined with an analysis of the synovial fluid, whenever possible, to rule out differential diagnoses such as infection, osteoarthritis or crystals.[40–42 48 66 67 75–77 122–126] If symptomatic treatment is insufficient and tissue inflammation is still evident, systemic glucocorticoids should be considered for both immune-related rheumatic and systemic symptoms. Overall, systemic glucocorticoids were used for 224/296 patients (76%) with arthritis[39–44 46 48 51 52 65–74 76–78 83 116 122 123 125–143] with a median dosage of 20 mg/day, for 37/65 patients (57%) with sicca syndrome[39 40 65 66 85–89] with a median dosage of 40 mg/day (16 patients for sicca symptoms, 15 patients for systemic manifestations or associated arthritis, 6 patients for sicca symptoms and associated other irAE), for 22/29 patients (76%) with vasculitis[48 84 103–106 108–112 144–150] with a median initial dosage of 60 mg/day, for 15/33 patients (45%) with sarcoidosis[39 44 91–93 151–158] with a median initial dosage of 55 mg/day, for 7/7 patients (100%) with scleroderma[48 94–96] with an initial dosage of 1 mg/kg/day and for 4/13 patients (31%) with lupus.[98–101] Subacute cutaneous lupus was mainly treated with topical steroids.[97] Treatment of patients with myositis is reported in a separate statement (*point to consider 8*).

So far, there are reassuring data regarding the use of glucocorticoids for irAE management.[159 160] For rheumatic irAEs, patients receiving glucocorticoids equivalent to 10 mg/day of prednisolone for 6 weeks concurrent to anti-PD1 therapy had a similar antitumour response.[77] However, recent preclinical data point out that glucocorticoids markedly impair the activation and the killing ability of tumour-infiltrating lymphocytes.[161] Because of concerns of glucocorticoids on antitumour responses, the task force did not recommend using methylprednisolone pulses or high-dose oral glucocorticoids in the absence of life-threatening complications and myositis, even in severe presentations, and favoured the concept of glucocorticoid sparing where rheumatologists have extensive experience with alternative options. Furthermore, the task force members recommended tapering glucocorticoids to the lowest effective dose within weeks or as soon as improvement is achieved was desirable. The objective of reaching a dose less than or equal to 10 mg/day of equivalent prednisone was considered as an acceptable target dose. This target dose as maintenance therapy is based on current preclinical and retrospective clinical data,[161–163] and higher than the one recommended for the main classical RMDs (online supplementary table S2).

5. csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing (LoE 4; LoA 9).

In case of active rheumatic irAE requiring dose of glucocorticoids higher than 10 mg/day of equivalent prednisone, conventional synthetic disease-modifying antirheumatic drug (csDMARD) should be considered. Several csDMARDs have been used as second-line therapy in the case of an insufficient response to glucocorticoids or for use as steroid sparing agents. So far, no specific biological disease-modifying antirheumatic drug has proven superiority. For the various types of arthritis in cases reported, methotrexate was the most frequently drug prescribed, followed by hydroxychloroquine then sulfasalazine, either as monotherapy or in combination.[39–41 43 44 48 51 52 65–67 69 70 75–78 122 123 125 128 131 132 134 140–142 164 165] Of note, no safety issues were described regarding long-term use of methotrexate associated with CPI in a few patients, with a median follow-up of over 1 year.[67] It is noteworthy that a higher proportion of hypersensitivity reactions were reported with sulfasalazine in the context of CPI-induced inflammatory arthritis, suggesting caution to its use in those situations.[165] One case series reported the initiation of hydroxychloroquine prior to glucocorticoids, limiting glucocorticoid exposure, which would deserve further evaluation.[166] The use of csDMARDs has not been described for patients with CPI-induced sicca syndrome. Two patients received hydroxychloroquine and one the combination of hydroxychloroquine and methotrexate for cutaneous leucocytoclastic vasculitis.[103] One patient with granulomatosis with polyangiitis was treated with oral cyclophosphamide.[105] For other systemic manifestations, hydroxychloroquine was safely prescribed for patients with CPI-induced lupus and scleroderma and in one patient with sarcoidosis.[48 95–100 157] Four patients with scleroderma-like syndromes received mycophenolate mofetil.[48 94 96] Among them, two also received intravenous immunoglobulin. Finally, two patients with neurosarcoidosis were successfully treated with methotrexate after an infusion reaction to infliximab.[92 93]

6. For patients experiencing severe rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis (LoE 4; LoA 8.8).

Gastroenterologists have safely and successfully administered infliximab for patients with severe CPI-induced colitis who had an insufficient response to glucocorticoids.[167 168] Based on these data, tumour necrosis factor (TNF) inhibitors (infliximab prevailing on etanercept and adalimumab) have been reported for severe and refractory inflammatory arthritis.[65 66 116 123 138] However, while patients experiencing colitis required one or two infliximab infusions, patients with arthritis may require long-term administration of TNF inhibitors, which is an important difference of unclear clinical significance at this time. A recent study reported that antitumour responses were not adversely affected in patients treated with TNF inhibitors, with a median follow-up of 9 months, but further data are needed.[169] Preclinical data support the use of TNF inhibitors, since infliximab only had a minor influence on T-cell activation and the killing ability of tumour-infiltrating lymphocytes, whereas even low doses of glucocorticoids markedly impaired this antitumour activity.[161] Furthermore, a synergistic effect of TNF inhibitors with CPI has been demonstrated in mouse models.[170 171] A phase I investigator-initiated trial (TICIMEL, NCT03293784) is currently testing the safety of this combined approach (double immunotherapy plus TNF inhibitor) in patients with melanoma. Results of this study will likely inform the management of rheumatic irAEs. The use of infliximab was also reported in two patients with neurosarcoidosis.[92 93]

There are also several observations in patients with CPI-induced inflammatory arthritis treated with tocilizumab.[48 52 68 83] Notably, one patient responded to tocilizumab after infliximab failure.[52]

Regarding interleukin 17 blockade, the use of secukinumab has been reported in a patient with mismatch-repair-deficient metastatic colon cancer and a previous history of Crohn's disease who experienced colitis, severe psoriatic rash and arthralgia.[172] While providing a dramatic relief of the immune-related skin, rheumatic and gastrointestinal side effects, subsequent tumour progression was observed. A second recent publication described the complete resolution of pembrolizumab-induced psoriasiform eruption with secukinumab in a patient with melanoma, without impact on tumour response.[173] Due to limited data and concerns about interleukin 17 inhibition on CPI efficacy, the task force agreed not to recommend interleukin 17 blockade for inflammatory arthritis.

For mechanistic reasons, abatacept should also not be considered for the treatment of CPI-induced rheumatic and systemic diseases, owing to the hypothetical risk of antagonising antitumour responses of CPI. However, one may consider its use in cases of life-threatening conditions, as discussed in the statement for myositis (*point to consider 8*).

One patient with neuro-Sjögren's syndrome was successfully treated with rituximab after intravenous pulses of methylprednisolone, immunoglobulins and one dose of cyclophosphamide.[87] Rituximab was also used in one patient with acral vasculitis without improvement and the need of surgical amputation.[105]

7. The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient (LoE 5; LoA 9.4).

Currently, decisions regarding CPI and immunosuppressive regimens vary from institution to institution according to local practice, with no randomised trials to provide evidence in choosing between holding CPI and/or introducing an immunosuppressive regimen. Overall, the SLR revealed that CPIs were discontinued in 25% of patients experiencing inflammatory arthritis, 61% of patients with sicca syndrome (a discontinuation of CPI often due to another associated irAE), 80% of patients with vasculitis, 64% of patients with sarcoidosis, 75% of patients with scleroderma and 78% of patients with lupus. It is noteworthy that several studies reported ongoing clinical benefit in patients who discontinue their cancer immunotherapy for irAEs.[7 174 175] Well-designed prospective trials will be required help to clarify the optimal immunosuppressive regimens.

8. Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary (LoE 4; LoA 8.9).

Myositis belongs to the spectrum of potentially fatal toxicity associated with CPI, since it is frequently associated with myocarditis and/or myasthenia gravis.[176–178] Notably, it generally occurs very early after CPI initiation, often within the first month of treatment (median exposure time of 25 days, IQR 25–45 days). Proximal weakness and myalgia are the major symptoms, which can mimic a PMR-like condition.[81] Therefore, a high awareness for myositis is needed among rheumatologists with measurement of creatine kinase (CK) since increased CKs are seen in the majority of patients with myositis (median of 2650 IU/L, ranging from 335 to 20 270 IU/L).[48 77 81–83 100 117 179–207] Of note, CK levels are usually within the normal range in patients presenting with myalgia.[42 83] Ptosis and diplopia are also commonly reported and may be related to associated myasthenia gravis.[81 82 100 117 184 185 189 191 192 195 197 198 204 205 208–210] Of note, some patients present with dropped head syndrome.[82 198 211] Importantly, one should search for the presence of life-threatening manifestations, including dyspnoea, palpitations, chest pain or syncope, which should alert on a possible concurrent myocarditis.[39 48 77 81–83 117 177–179 182 184 185 187 190 193 200 207 211–215] Of note, an increased risk of death in patients experiencing CPI-related myositis has been observed compared with patients with idiopathic inflammatory myositis (around 20% vs less than 10%).[177 216] This increased mortality rate seems to be related to the development of myocarditis. While there is no standardised assessment of myocarditis in large series of idiopathic inflammatory myopathy, signs of myocardial inflammation cardiac has been reported on magnetic resonance tomography in more than 60% of such patients,[217] which argue that myocarditis belong to the myositis clinical spectrum and does not represent a different concomitant irAE. Therefore, cardiac evaluation must be systematic for any patient with myositis or suspected myositis. It includes cardiac troponin (troponin T is less specific than troponin I in case of associated skeletal muscle diseases) and electrocardiography. In case of clinical syndrome associated with myocarditis and/or increase cardiac troponin level and/or electrocardiography, a cardiac MRI is necessary.[218] Of note, normal cardiac enzyme cannot always rule out the possibility of myocarditis. Furthermore, the presence of bulbar symptoms (dysphagia, dysarthria, dysphonia) and/or respiratory failure may be related to myositis or associated myasthenia gravis encountered in 12.5% of patients (57/454 cases reported).[82 83 100 177 178 186 188 189 192 195 203 204 208 211 212] Of note, the majority of patients will not have a typical skin rash of dermatomyositis, only reported in a few patients.[199 201 219]

Myositis-associated autoantibodies are mostly negative, though cases with positive ANA, antistriated antibodies, anti-PM/Scl, anti-SM, anti-TIF1 gamma, anti-PL-7, anti-PL12, anti-Jo1 or anti-SRP have been reported.[77 83 117 184] Electrodiagnostic studies usually reveal myopathic pattern with musculature enhancement may be observed on MRI. Biopsy is often performed and confirms muscle damage with variable degrees of inflammatory and necrotic changes.[81] Of interest, fasciitis is also increasingly reported clinically and seen on MRI findings.[40 76 220–224]

Prompt recognition and early management of myositis is imperative. Discontinuation or at least interruption of CPI was reported in more than 85% of patients and is mandatory in the presence of dyspnoea, bulbar symptoms, severe muscle weakness and/or myocarditis. High-dose systemic glucocorticoids are the first-line treatment, usually 1–2 mg/kg/day (median dosage 70 mg/day). Ten per cent of reported patients received intravenous pulses of methylprednisolone. Up to 20% of patients also received intravenous immunoglobulins,[39 48 77 81–83 181 183–185 188 189 191 198 201 207–209 211 212 220 225 226] and plasma exchanges were performed in around 10% of patients.[48 81 82 117 150 184 188 189 191 197 204 205 226] As second-line therapy, several csDMARDs have been used: mycophenolate mofetil,[77 209 225] methotrexate,[39 44 77 81] azathioprine in one patient but stopped for pancreatitis[77] and hydroxychloroquine in one patient.[76] Six patients have been treated with infliximab, but only one successfully.[82 182 184 225] Importantly, a recent publication reported the resolution of a severe glucocorticoid-refractory myocarditis with abatacept, received after plasma exchanges was unsuccessful.[227] Another T-cell directed therapy, alemtuzumab, has been successfully used in a patient with glucocorticoid-refractory myocarditis.[228] The task force agreed that further evaluation is warranted, most notably on the impact on tumour response; however, due to the lack of effective therapy and the high mortality rate of myositis complicated with myocarditis or severe respiratory failure, one may consider their use as rescue therapy in refractory situations.

9. A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs (LoE 4; LoA 9).

Patients with pre-existing inflammatory or autoimmune disease have been largely excluded from clinical trials due to the theoretical risk of worsening autoimmune manifestations. However, there are several series reporting on CPI safety in such patients, with either anti-CTLA-4[229–231] or anti-PD-(L)1 .[77 232–235] Together, a flare of the pre-existing inflammatory or autoimmune disease was observed in half of patients with RA (47/86 patients), PsA (4/8 patients) and myositis (1/2 patients), 64% of patients with PMR (16/25 patients), 31% of patients with SA (4/13 patients) and patients with systemic lupus erythematosus (4/13 patients), 43% of patients with Sjögren's syndrome (3/7 patients), 25% of patients with systemic sclerosis (2/8 patients) and 20% of patients with sarcoidosis (3/15 patients), but less than 10% had to stop CPI therapy during a flare. The patient with pre-existing giant cell arteritis experienced a relapse. There was no flare reported for the few patients with pre-existing seronegative arthritis (n=4), other vasculitis (n=4) and Behçet's disease (n=1). Furthermore, 18 of 104 patients (17%) experienced other irAEs, mainly colitis (n=12), hypophysitis (n=3) and thyroiditis (n=3). One patient with RA developed myositis requiring high dose of glucocorticoids and intravenous immunoglobulins, and another patient with RA developed Sjögren's syndrome with autoantibodies (ANA 1/1280, anti-SSA and SSB). Overall, CPI was discontinued in 8% of patients with pre-existing autoimmune disease due to other irAEs, unrelated to their pre-existing autoimmune disease. In a recent case series of 112 patients with pre-existing autoimmune diseases treated with CPI, a flare of pre-existing autoimmune disease or another irAE occurred in 71% of the patients (47% has a flare of their pre-existing disease and 43% had another irAE).[236] Thus, the occurrence of a flare/irAE was frequent but mostly manageable without CPI discontinuation in 79% of the patients.

In these case series, most flares and irAEs were managed with glucocorticoids, with the need of csDMARDs in some patients, usually hydroxychloroquine, methotrexate, sulfasalazine, either in monotherapy or in combination. The need for TNF inhibitors was only reported in patients with flares of their inflammatory bowel disease flares and in two cases of new-onset colitis. Based on these data, the task force agreed that CPI therapy in patients with pre-existing autoimmune rheumatic and systemic disease was not contraindicated, provided that the patient is well-informed and closely monitored. No preventive treatment is needed. Importantly, this remains a shared decision between the oncologist, rheumatologist and the patient, and whether CPI will be used in a metastatic or adjuvant setting is a major aspect to be considered.

Regarding baseline immunosuppressive regimen, recent preclinical and clinical data highlighted the deleterious impact of baseline glucocorticoids on CPI efficacy, when used at a dosage of greater than 10 mg/day.[163 237] However, this was in patients treated with steroids for their cancer or cancer-related symptoms and not for autoimmune symptoms. Accordingly, the task force agreed on recommending the lowest immunosuppressive regimen possible at the start of CPI therapy. However, future data on prophylactic TNF inhibition and a possible synergistic effect of TNF inhibitors and CPI, reported in a mouse model and currently evaluated in patients, may challenge this statement over time.[171]

10. Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatologic assessment should be performed (LoE 5; LoA 9).

Analysis of pretreatment and post-treatment sera of anti-CTLA4-treated patients with melanoma revealed that for most autoantibodies, including RA-associated antibodies, post-treatment titres increased only marginally and were not associated with the occurrence of irAEs.[238] Similarly, the presence of ANA in serum collected prior to initiating CPI therapy was not found to predict the development of irAEs, except for colitis.[239 240] One study reported divergent data, with pre-existing antibodies independently associated with the occurrence of irAEs, but also with clinical benefits on advanced non-small cell lung cancer.[241] Notably, skin reactions were more frequent among patients with pre-existing RF.

Since autoantibodies are not found in the majority of patients experiencing CPI-induced rheumatic and systemic disease, there is no indication to test every patient at baseline. Of note, the presence of ACPAs has been detected in serum samples obtained prior to CPI therapy in few patients who experienced RA and were asymptomatic before the start of CPI.[78] But this situation might be rare, and the detection of autoantibodies in an asymptomatic patient would not preclude the start of CPI therapy. However, there is the particular situation of patients with thymoma who develop CPI-induced myositis and who all have anti-acetylcholine receptor and antistriated muscle antibodies detected in serum sample obtained prior to CPI therapy.[179] Accordingly, as myositis may evolve into a severe irAE, testing for the presence of these antibodies before starting CPI in a patient with thymoma is recommended to identify a high risk of myositis.

CONCLUSION

These points to consider provide the basis of an European League Against Rheumatism consensus on the diagnosis and the management of rheumatic and systemic irAEs which represent a new and rapidly expanding field. The task force aimed to raise awareness and to assist rheumatologists to improve the diagnosis and the management of patients with irAEs. In contrast to other irAEs, rheumatic irAEs frequently persist over time, specifically inflammatory arthritis was persistent in almost 50% at most recent follow-up with a median of 9 months in a recent study.[169] Thus, irAEs represent a new spectrum of RMDs that rheumatologists should familiarise with. Interestingly, many of these manifestations, either frequent (arthritis, myositis, sicca syndrome) or more exceptionally reported (scleroderma, lupus) are also characteristics of graft versus host disease.[242] Early consultation and strong collaboration between the referring oncologist, the treating rheumatologist, potentially other organ specialists and the patient are all required for optimal irAEs management.

These statements, being based almost entirely on low levels of evidence and on experts opinion, will undoubtedly require updating over the next few years, as new data emerge. Indeed, we expect that future oncological data will likely impact our irAEs therapeutic strategy. We also anticipate a better understanding of irAEs mechanisms and pathophysiology. Finally, multicentre collaborative efforts, prospective registries and randomised trials will help to define the optimal treatment strategies to relieve patient symptoms without altering oncological outcomes.

RESEARCH AGENDA

- To better understand pathophysiology of rheumatic and systemic irAEs.
- To develop information on rheumatic and systemic irAEs for patients starting cancer immunotherapy.
- To define optimal glucocorticoid dose and duration according to the type of rheumatic and/or systemic irAE.
- To assess the effect of different immunomodulatory/immunosuppressive agents already given before the start

of CPI therapy in pre-existing RMDs on the outcome of immunotherapy.
- To assess the effect of different immunomodulatory/immunosuppressive agents administered for de novo rheumatic and systemic irAEs on the outcome of immunotherapy, using prospective registries.
- To develop well-designed trials on irAE management.
- To assess long-term evolution of rheumatic and systemic irAEs.
- To search for predictive factors for rheumatic and systemic irAEs.
- To revise CTCAE grading of rheumatic and systemic irAEs.
- To obtain insights on the initiation and propagation of classical rheumatic diseases.

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Acknowledgements The task force gratefully thank the librarian Catherine Weill (Bibliothèque Inter-universitaire de Santé, Paris, France) for her contribution to the systematic literature search, and European League Against Rheumatism for financial and logistical support.

Contributors The paper was drafted by MK, XM, AF and TS and all authors contributed with specific comments and revisions to the paper.

Funding This study was funded by European League Against Rheumatism (grant no: CLI106).

Competing interests MK: honoraria from Abbvie, BMS, Lilly, Novartis, Pfizer; TRDJR: grants from AbbVie, Takeda, UCB, Janssen, GSK and honoraria from Abbvie, Pfizer, Takeda, Lilly, Medimmune, Novartis, GSK, BMS, AstraZeneca, Janssen; XM: honoraria from BMS; COB: grants and honoraria from BMS and honoraria from Genetech/Roche, Sanofi/Regeneron; OL: grant from Gilead and honoraria from BMS, MSD, AstraZeneca, Janssen; JLe: grants from Novartis, Pfizer and honoraria from Abbvie, AstraZeneca, BMS, Celgene, Hospira, Janssen-Cilag, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB; AM: grants from BMS, Merus and honoraria from Merck Serono, Lytix, BMS, Symphogen, Amgen, AZ/Medimmune, Servier, Gritstone, Pierre Fabre, EISAI, Sanofi; TS: honoraria from Pfizer, Lilly, Novartis, BMS, Abbvie, Sanofi; EHC: grants from Biogen, grants and honoraria from Amgen, Bio-Cancer, Roche, UCB, Pfizer, honoraria from Chugai Pharma, Abbvie, BMS, Celgene, Eli Lilly, Janssen, ObsEva, Regeneron, Sanofi, SynAct Pharma, Tonix, Gilead; LT: honoraria from Novartis; KB: grants from Abbvie, Novartis, Rheumaliga Baden-Württemberg and honoraria from MSD, Abbvie, BMS, Janssen, Lilly, Mundipharma, Novartis, Pfizer, Roche, UCB; KV: speaker fees from BMS; JLa: grants from Aveo and Pharmacyclics, grants and honoraria from Achilles Therapeutics, MSD, Nektar, Novartis, Pierre Fabre, Pfizer, Roche/Genetech and Immunocore, honoraria from AstraZeneca, Boston Biomedical, BMS, Eisai, EUSA Pharma, GSK, Ipsen, Imugen, Incyte, iOnctura, Kymab, Merck Serono, Secarna, Vitaccess and Covance; JBAGH: grants from BMS, Novartis and advisory boards and/or lectures for MSD, BMS, Roche, Novartis; J-EG: grants from BMS, UCB, Pfizer, Sanofi and honoraria from BMS, Lilly, Pfizer, Sanofi-Genzyme, UCB.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information

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