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Unmet need in rheumatology: reports from the Advances in Targeted Therapies meeting, 2023

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ABSTRACT

The Advances in Targeted Therapies meets annually, convening experts in the field of rheumatology to both provide scientific updates and identify existing scientific gaps within the field. To review the major unmet scientific needs in rheumatology. The 23rd annual Advances in Targeted Therapies meeting convened with more than 100 international basic scientists and clinical researchers in rheumatology, immunology, infectious diseases, epidemiology, molecular biology and other specialties relating to all aspects of immune-mediated inflammatory diseases. We held breakout sessions in five rheumatological disease-specific groups including: rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpa), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and vasculitis, and osteoarthritis (OA). In each group, experts were asked to identify and prioritise current unmet needs in clinical and translational research. An overarching theme across all disease states is the continued need for clinical trial design innovation with regard to therapeutics, endpoint and disease endotypes. Within RA, unmet needs comprise molecular classification of disease pathogenesis and activity, pre-/early RA strategies, more refined pain profiling and innovative trials designs to deliver on precision medicine. Continued scientific questions within *PsA* include evaluating the genetic, immunophenotypic, clinical signatures that predict development of PsA in patients with psoriasis, and the evaluation of combination therapies for difficult-to-treat disease. For axSpA, there continues to be the need to understand the role of interleukin-23 (IL-23) in pathogenesis and the genetic relationship of the IL-23-receptor polymorphism with other related systemic inflammatory diseases (eg, inflammatory bowel disease). A major unmet need in the OA field remains the need to develop the ability to reliably phenotype and stratify patients for inclusion in clinical trials. SLE experts identified a number of unmet needs within clinical trial design including the need for allowing endpoints that reflect pharmacodynamic/functional outcomes (eg, inhibition of type I interferon pathway activation; changes in urine biomarkers). Lastly, within SSc and vasculitis, there is a lack of biomarkers that predict response or disease progression, and that allow patients to be stratified for therapies. There remains a strong need to innovate clinical trial design, to identify systemic and tissue-level biomarkers that predict progression or response to therapy, endotype disease, and to continue developing therapies and therapeutic strategies for those with treatment-refractory disease. This document, based on expert consensus, should provide a roadmap for prioritising scientific endeavour in the field of rheumatology.

BACKGROUND

The Advances in Targeted Therapies meeting (ATT) met annually for 21 years prior to the SARS Co-V-2 pandemic. The meeting returned in smaller format in March 2022, and finally in full form in March 2023 in Nice, France. This meeting convenes international experts working within inflammatory disease, including clinical scientists, molecular biologists, immunologists, epidemiologists and other experts ultimately contributing to the prevention, diagnosis and treatment of rheumatic and musculoskeletal diseases. The meeting focuses on the clinical and translational aspects of immune-mediated inflammatory diseases (IMIDs) with invited faculty delivering talks within their respective areas of expertise and providing updates regarding disease mechanism(s) and pathophysiology, and recent developments with both existing and novel targeted therapies in IMIDs. Distinct from the year prior, in which discussion around COVID-19 and its relationship to rheumatology dominated, the meeting focus returned to the traditional aspects of basic and clinical science of rheumatic diseases.

METHODS

As in prior years, all conference participants were divided along their subject matter expertise to take part in the following disease-specific breakout groups: rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), systemic lupus erythematous (SLE), systemic sclerosis/vasculitis, and for the first time this year, osteoarthritis (OA). Each group was led by a facilitator and rapporteur who guided discussion within the areas of translational science, clinical care, and therapeutic development. Groups were asked to identify and then prioritise current unmet needs within these areas, as well as highlighting recent progress in meeting previously identified unmet needs.

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It should be noted that the articulated and discussed unmet needs are but a selection, and that many others exist (eg, comorbidity management, adherence, others) that were not necessarily discussed due to the limited time of the meeting.

RESULTS

Rheumatoid arthritis

Unmet needs discussed 12 months ago included the need to better understand the progression from pre-RA to clinical disease, and the triggers of progression, particularly to facilitate the design of prevention studies. At that time, it was acknowledged that a better understanding of refractory disease was also required, especially at the molecular level. Recent observations suggested that flares of RA, in patients with periodontal disease, are associated with repeated breaches of the oral mucosa that release bacteria into the bloodstream.[1] This is associated with monocyte activation, as well as potentially providing a source of citrullinated antigen to the immune system, and may therefore also have relevance to the transition of pre-RA to RA. The Abatacept reversing subclinical Inflammation as measured by MRI in ACPA positive Arthralgia (ARIAA) trial is the latest RA prevention study to report, although so far only in abstract form. It demonstrates that a 6-month intervention with abatacept in anti-citrullinated protein antibody (ACPA)-positive individuals with joint inflammation on MRI, reduces the inflammation and, furthermore, delays the development of RA when compared with placebo.[2] Whether it can prevent RA development awaits further data from the study. In terms of refractory RA, a deep dive into data from the R4RA study linked a fibroblast molecular signature to synovitis that failed to respond to three biological drugs.[3] It is not yet known whether this form of fibroblastic synovitis had emerged over time or was present at disease inception.

The heterogeneity of RA continues to complicate studies of pathophysiological and molecular mechanisms of synovial inflammation. Contrasting with oncology, where the pathogenic cell is usually well characterised, and driven by small number(s) of penetrant, and sometimes targetable, mutations, RA is highly heterogeneous with many variable and small impact polymorphisms, along with environmental stimuli, influencing the ultimate evolution. Thus, while understanding pathophysiological changes in response to treatment remains a major focus of current research activities, there is a clear need for a more granular classification of disease pathogenesis and activity that can help to identify precision medicine targets and strategies, beyond the currently used metrics for clinical, imaging, serological and histological data.[4] There is positive progress, for example, in the definition of cell type abundance phenotypes[5] but linking these cellular definitions to specific pathophysiological subtypes of disease remains to be elucidated. A further challenge is to use the best methodological metrics to select homogeneous patient populations for interventional studies. Is a synovial biopsy needed to determine disease categorisation or will clinical parameters suffice? And if a synovial biopsy is needed, how reliant can the clinician be on pathological and molecular features in a single joint, at a single time point? Ultimately, will there be a minimum molecular or imaging criterion that can be used to define subsets of RA? Synovial biopsies may be particularly pertinent to studies of remission. At present, clinical definitions of remission are poorly used—the group felt strongly that the American College of Rheumatology-European League Against Rheumatism definition[6] was underused, instead many studies use less stringent definitions based, for example, on Disease Activity Score 28 (DAS-28) . Similarly, when performing biopsy studies, it is important to understand whether there are molecular correlates of clinical remission. Do these reflect an absence of a 'minimum molecular or imaging criterion', essentially reflecting normal synovium, or is remission expected to reflect more of a 'regulated' state of subclinical inflammation, as suggested by some recent studies?[7] There was an emerging sense that remission does, in fact, reflect a state of disease regulation rather than an 'absence of disease'. The achievement of drug-free remission in a proportion of patients with recent-onset RA suggests that the immune-pathological abnormalities may be reversible, and subsequent flares in a proportion of patients reinforce the continued presence of disease propensity, suggesting regulation rather than a return to normality.[8] A further question is whether flares under such circumstances recapitulate the early phases of clinical RA. In summary, the group agreed on the importance of utilising appropriate and stringent clinical metrics for patient selection in studies of disease pathophysiology, in order to subsequently precisely define molecular states of pathophysiology and disease activity, including remission or disease flare.

A major breakthrough in recent years is the increasing utilisation of artificial intelligence (AI) and machine learning (ML) to deal with the large amounts of data being generated and deposited, often in publicly accessible datasets.[9] In many ways, the challenges link to those discussed above, as many databases currently remain highly heterogeneous and outputs rely heavily on the quality of the data and metadata. Current efforts to attempt to address these issues sometimes link large heterogeneous datasets with smaller but highly detailed and focused datasets. The small and detailed datasets can then be used to generate hypotheses and ideas, which can then be tested on the larger but less refined datasets. Ultimately, however, the increasing complexity and large number of variables available for analysis, for example, in single-cell synovial databases, requires the 'best of both worlds'—large numbers of deeply characterised samples, curated from homogeneous and well stratified patient populations.[10] Furthermore, longitudinal data are currently sparse and yet critical if we wish to use computational ML approaches to adequately address precision medicine questions. This longitudinal data are critical in order to link intervention and outcome, both in terms of clinical and molecular data. Also needed are teams with computational scientists and bioinformaticians as core members, where these do not already exist, to advise and guide on on approaches from concept through to analysis. In this way, understanding and using high-dimensional data analysis of many different cell populations may facilitate the discovery of the aforementioned critical biomarkers in RA research, providing molecular definitions of disease pathophysiology and activity to partner with current clinical endpoints. It was recognised by the group, however, that such an ambition will require a willingness of groups around the world to collaborate, adhering to agreed protocols and endpoints. Nonetheless, contrasting with such large-scale observational approaches there is also huge value in smaller scale, hypothesis-based and discovery-driven, experimental medicine approaches.[11] These should complement, and be informed by, the larger scale hypothesis-generating studies. Such studies can use similar multidimensional and molecular techniques but on smaller and precisely-defined patient cohorts, for example, procuring biopsies before and after perturbation of the system by an experimental intervention such as a therapy. In addition to addressing the primary outcome, these studies themselves can generate further hypotheses. In summary, the multidimensional data that it is now possible to generate requires robust AI and ML approaches for its maximal exploitation.

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While such hypothesis-generating work requires significant collaboration and agreement to ensure high-quality outputs, experimental medicine approaches can exploit the same technologies and analytical approaches to address hypotheses, while also providing rich data in their own right and generating further ideas.

In conclusion, it is well recognised that RA is a heterogeneous disease with discrete subsets. Precision medicine approaches aim to categorise RA into more homogeneous subsets, targetable by distinct classes of intervention. Increasingly sophisticated molecular techniques, along with AI and ML methodologies, should help to achieve this goal, ably assisted by more focused experimental medicine approaches. Clinicians and clinician scientists, however, cannot afford to lose sight of their patients and their symptoms, ensuring that these sophisticated approaches are applied to well-defined and clinically homogeneous patient groups, using stringent and clinically relevant disease activity and outcome measures.

Psoriatic arthritis

During 2022 and early 2023, a number of advances in the field of PsA have occurred which reflect progress in meeting some of the issues identified in the 'unmet needs' statement from ATT 2022.[12] PsA comprises a number of different clinical domains which manifest their own unique clinical features and immunophenotypes, including arthritis (synovitis), enthesitis, dactylitis, spondylitis, psoriasis and nail disease. Particular recent focus has been placed on axial PsA which demonstrates significant differences from axSpA when viewed through the lenses of genetics, clinical phenotypes, imaging features, natural history and treatment response.[13] In the past year, the AXIS study has become half enrolled.[14] AXIS is a collaborative study between the key research and education associations, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Anklosing Spondylitis Acitivity Score (ASAS). Over 400 biologically naive patients with PsA who have centrally adjudicated axial disease and a similar number without axial disease are being enrolled with the intent to derive classification criteria for axial PsA from the clinical, laboratory and imaging phenotype of the AXIS participants. In parallel, a study being conducted by the GRAPPA Collaborative Research Network has begun enrolling patients with PsA and axial PsA, but additionally including numerous blood samples for immunophenotyping for genomics, proteomics and metabolomics, skin and synovial biopsies, and stool for microbiome analysis, to better understand the 'molecular' differentiation of PsA with and without axial involvement. Lastly, the STAR trial is actively enrolling patients with MRI-imaging defined axial PsA to determine the effectiveness of guselkumab, a p19 IL-23 inhibitor, for this condition.

2022 has seen the advancement of new molecular entities in the treatment of PsA. Successful phase 2 trials of TYK2 inhibition, deucravacitinib (TYK2i)[15] and brepocitinib (TYK2/JAK1i)[16] have been completed, with phase 3 trials of deucravacitinib underway. Furthermore, the US Food and Drug Administration (FDA) has approved deucravacitinib for the treatment of psoriasis, without the black box warning about adverse cardiovascular and malignancy effects required for other JAK inhibitors nor the requirement to use the drug after TNFi use, signalling regulatory agency differentiation of risk among the JAK class of drugs. Several other TYK2i are in development. A successful phase 2 PsA trial of an IL-17A inhibitor nanobody construct, izokibep, has been presented, with phase 3 study underway.[17] The nanobody is approximately a tenth the size of a standard monoclonal antibody. This small size, along with inclusion of an albumin-binding domain to increase plasma half-life, may result in deeper tissue penetrance in difficult to target anatomical sites such as entheses. If this is shown to be successful, then more drugs using this technology, with different molecular targets, may be developed in the future. A similar construct targeting both IL-17A and F (sonelokimab) is currently in a phase 2 trial in PsA, after completing a successful phase 2b trial in psoriasis.[18] A monoclonal bispecific antibody targeting IL-17A and F, bimekizumab, is currently approved for psoriasis and PsA in several countries and is pending approval in other countries.[19 20]

There is need for better definition of and novel treatment approaches for 'difficult-to-treat'(D2T) PsA, similar to a project that has been completed for RA and is currently underway for axSpA. GRAPPA has formed a working group to come up with a definition of D2T, such as recurring and persistent active disease despite treatment with several classes of medications, and distinguishing these patients with true 'refractory' PsA from patients whose symptoms may be arising largely from comorbidities such as fibromyalgia and OA. Such a definition will help clinicians, clinical trial designers, payors and regulatory agencies address the unmet need for novel therapeutic approaches such as the simultaneous use of two biologics or a biological and targeted synthetic disease-modifying drug with different mechanisms of action to more completely inhibit proinflammatory activity across disease domains in PsA. A trial, AFFINITY, using this approach is underway, comparing the IL-23 inhibitor, guselkumab in combination with a TNF inhibitor, golimumab, versus guselkumab or golimumab alone in PsA patients who have had inadequate response to at least one TNF inhibitor. There are an increasing number of case series with these types of combinations being reported. One key question to be assessed in observational registries and clinical trials: 'Is this combination safe and is it efficacious compared with monotherapy?'. Part of the spectrum of D2T is the patient who has both PsA and inflammatory bowel disease or uveitis, or within the psoriatic disease clinical spectrum is experiencing differential response of psoriasis lesions and musculoskeletal manifestations. These patients may benefit from pairing a medication which is more effective in the intestine or skin, for example, with one that is more effective for musculoskeletal disease, the former prescribed by a dermatologist or gastroenterologist and the latter by a rheumatologist working together. This approach requires close communication and collaboration between clinicians in different specialties.

Although a few head-to-head clinical trials have been completed in PsA, providing evidence for comparative efficacy and safety of therapies with different mechanisms of action,[21–23] there is a paucity of such evidence compared with other disease states such as psoriasis and RA. Instead, we are observing more network meta-analyses and matching-adjusted indirect comparison studies being done to provide indirect comparisons to help guide clinicians in therapeutic decision-making, as well as payors and administrative bodies.[24–27]

Numerous other research questions are actively being pursued by research groups including large EU (HIPPOCRATES) and US (AMP AIM) consortia. These questions include evaluating the genetic, immunophenotypic and clinical signatures that predict development of PsA in patients with psoriasis, identifying approaches that can prevent this transition from occurring, identifying biomarkers that can predict which treatment mechanism will be most effective in a specific patient, allowing a 'precision medicine' approach to therapeutic decision-making and understanding the specific immunophenotypes of the principal tissue domains of PsA, including how these drive chronicity.

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Axial spondyloarthritis

In 2023, the discussion group dedicated to axSpA discussed the unmet needs that were identified in 2022[12] and evaluated the progress in the field over the past year based on these. A major topic of discussion was still the role of IL-23 and its role in the development of axSpA.[28] This discussion also referenced the genetic relationship of the IL-23-receptor polymorphism to systemic inflammatory diseases, such as axSpA or inflammatory bowel disease. This discussion may be relevant to the separation of different phenotypes of spondyloarthritis (SpA), for example, the phenotype with or without involvement of the peripheral skeleton or with or without extramusculoskeletal manifestations and the different effects of biologics or targeted synthetic DMARDs on these phenotypic manifestations. The group identified the important gap in knowledge especially in the role of the gastrointestinal tract, which has become even more relevant after the positive[29] and the negative[30] results of studies with IL-17 and IL-23 inhibitors respectively on the symptoms of the axial skeleton.

It became clear that although the field of SpA in general has learnt a lot from the clinical studies about the pathophysiology of the disease, many open questions still remain. Information on pathophysiology may well be relevant for the understanding of previous negative studies with compounds which are effective in other inflammatory rheumatic diseases[31] but also for future studies of combinations of treatments.[32] Identifying the 'target issue' of each individual patient will perhaps provide a more individualised and effective treatment.

In addition, the group emphasised the unmet need to understand the differences of the disease phenotype and treatment effects in male and female patients. Such differences may be relevant not only for the choice of treatment but also the understanding of reporting disease activity (eg, responding to questionnaires) between males and females.

From a clinical perspective, the group felt that there is still a gap in clarifying the nomenclature in axSpA. The distinction between non-radiographic (nr-) and radiographic (r-) axSpA seems still not to be clear to physicians and patients. This distinction is rather arbitrary due to the low sensitivity and specificity of the conventional radiographs of the sacroiliac joints. It is also muddled by the use of classification criteria that are developed to select participants for clinical studies. While regulatory agencies still request these classifications for treatment approval, their application in daily practice does not make sense and should be avoided, especially due to the danger of misusage for diagnostic purposes.

Finally, the group recommended implementation of the (currently published) treatment recommendations,[29] including the need for more data on the effect of exercises on disease activity, and progression in daily practice/after diagnosis. These need special attention and should be part of the research agenda in the field of axSpA.

Osteoarthritis

OA is estimated to affect approximately 15% of adults, making it the most prevalent musculoskeletal disease globally. It is a highly heterogeneous disease that progresses slowly in the majority of individuals. Current therapeutic strategies (ie, symptom-modifying drugs) provide only modest responses, and there are no licensed drugs or biological agents with proven efficacy that can modify the disease process.[33] However, recent clinical trials have shown that it is possible to modify structural disease[34] and pain[35] or reduce rates of total hip and knee joint replacement.[36]

Post-traumatic OA occurs in around 50% of individuals following an acute destabilising injury to the joint. In these individuals, disease manifests within 5–10 years irrespective of surgical intervention,[37] making this group potentially more amenable for testing novel therapies. However, the pathogenic drivers of post-traumatic OA may not apply to the full spectrum of OA. Thus, there is also an urgent need to develop and study effective treatments for more generalised and age-related OA. Furthermore, the long duration of time over which OA evolves creates significant challenges for clinical trials.

Appropriate clinical trial design is essential to establish the therapeutic efficacy of new drugs in diseases in which there is substantial disease heterogeneity. The response to medications directed towards specific pathophysiological mechanisms may be underestimated if the population studied is not matched to the therapeutic mechanism of the drug. This is particularly relevant in OA, in which there might be multiple pathogenic mechanisms. Thus, a major unmet need in OA research is to develop reliable methods to phenotype and stratify patients for inclusion in clinical trials. Such phenotyping should include the assessment of symptoms such as pain, imaging outcomes and biomechanical function, and also molecular endotype assessments of circulating and joint tissue biomarkers. By enrolling subjects whose phenotype/endotype aligns most closely with the mechanism of action of the therapeutic agent being studied, clinical trials may require fewer patients and can be better powered to demonstrate specific outcomes. Thus, it is critically important to select relevant outcome measures for OA clinical trials. In addition to showing symptomatic improvement in pain and function, clinical trials of medications for OA should demonstrate structural improvement. However, given the length of time required to observe robust structural outcomes, markers that are surrogates for structural improvement are urgently needed for drug development such that trials of feasible duration are possible. Efficacy data should be aligned with relevant biomarkers that reflect the impact of the therapeutic agent on its target.

The incorporation of short experimental medicine studies into drug development programmes will provide an important opportunity to reduce risk of failure for future OA clinical trials. This approach is most valuable for studying molecular mechanisms that are well understood and when the biological processes are evident in tissue that is available for sampling. Experimental medicine studies can also be used to check target engagement and to identify the optimal dose of a drug at a molecular level by examining relevant tissues at early time points after treatment administration. Such tissues might include biopsied synovium, synovial fluid, or blood, although proximity of tissues and fluids to the diseased joint likely will be more informative. For early studies to validate a novel drug, for example, surgically obtained tissues might be assessed following delivery of a medication prior to joint surgery. Experimental medicine studies can also be used to identify subgroups of patients that respond best to a given treatment. This information can then be incorporated into clinical trial design, either by excluding patients who respond inadequately or by stratifying subjects based on this measure and assessing whether this approach to classification enriches the proportion of responders. Finally, experimental medicine studies have the potential to elucidate molecular mechanisms that might serve as future targets for drug discovery.

Developing drugs for OA remains challenging. Acceptable and clinically relevant improvement in pain and function might be achieved in clinical trials of relatively short duration, with a primary endpoint at 12 weeks, by using better validated outcomes of pain and function and by assessing patient global

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Table 1 Identified unmet research needs of high priority within RA, PsA, AxSpa, SLE, OA and systemic sclerosis and vasculitis

Rheumatoid arthritis	
	The establishment of precision medicine targets and strategies, as well as the identification of molecular correlates of clinical remission. This includes the use of artificial intelligence and machine learning to facilitate these objectives
Psoriatic arthritis	The evaluation of genetic, immunophenotypic and clinical signatures that predict PsA development, and the evaluation of combination therapies against difficult-to-treat disease Further head-to-head clinical trials evaluating comparative efficacy and safety of therapies with different mechanisms of action Better definition of and novel treatment approaches for 'difficult to treat' (D2T) PsA
Axial spondyloarthritis	The need to understand the role of interleukin-23 (IL-23) in AxSpa pathogenesis, and the need to understand the genetic relationship of the IL-23-receptor polymorphism with other related systemic inflammatory diseases (eg, inflammatory bowel disease). The need to understand the differences of disease phenotype and treatment effects in male and female patients
Systemic lupus erythematosus	Further refinements in clinical trial design including the need for allowing endpoints that reflect pharmacodynamic/functional outcomes (eg, inhibition of type I interferon pathway activation; inhibition of urine biomarkers), trial designs that target patients lacking high disease activity, and designs that incorporate measures of coronary and/or central nervous system disease. The need for specific treatments in refractory antiphospholipid syndrome.
Osteoarthritis	The need to develop the ability to reliably phenotype and stratify patients for inclusion in clinical trials. The urgent need to develop and study effective treatments for more generalised and age-related OA.
Systemic sclerosis and vasculitis	A need for biomarkers that predict response or disease progression, and that allow patients to be stratified for therapies. Building interdisciplinary (eg, rheumatology, nephrology, pulmonology, others) specialised care centres to foster research and to improve patient management

AxSpa, axial spondyloarthritis; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

responses.[38] Although measures of centrally mediated pain are available, these often are not incorporated into clinical trial protocols, which may result in underestimating a medication's efficacy. It remains important that the effect of study drug on these outcome measures achieves statistical significance and clinical relevance. Clinical trials of medications that modify disease progression by improving cartilage structure will require much longer periods of observation in order for the drug to receive regulatory approval. Acceptable surrogate endpoints would be of great utility. Composite endpoints, including items such as time to requiring total joint replacement and thresholds to identify severe levels of pain and functional disability, could be developed to reduce the sample size required for a clinical trial of reasonable duration.[39]

Systemic lupus erythematosus

There have been several recent advances in the areas of pathogenesis and treatment of SLE. First, improved understanding of the critical role of B cells in disease is highlighted by CAR T cell data (as well as data from anti-CD19 trials) that support the conclusion that effective depletion of B cells can achieve sustained clinical response, with remaining research needed to determine whether targeting CD19 depletes both plasmablasts and long-lived plasma cells or alternatively, whether depletion of the latter will be required for sustained clinical response in some patients.[40] Urine proteomics has the potential to serve as an actionable guide for assessment of disease activity and surrogate marker of response in lupus nephritis.[41] In addition, characterisation of distinct molecular pathways in patients with 'type 1' versus 'type 2' SLE supports the validity of the clinical features of type 2 disease (fatigue, fibromyalgia, etc) and points to some nerve and muscle-related molecular pathways as priorities for further investigation.[42] Shared susceptibility genes between SLE and cardiovascular disease deserve further investigation.[43] Lastly, the production of endogenous anti-type I interferon antibodies in some lupus patients was highlighted and their potential to confound assessment of the interferon pathway.[44]

Two new immunomodulatory drugs, voclosporin (calcineurin inhibitor) and anifrolumab (type 1 interferon receptor antibody), have recently been approved or have begun to be used in many countries.[45 46] Provocative and promising data from small studies of CD19 CART cells were discussed, raising the potential for 'cure' but also identifying the need for assessing the contribution of the cytotoxic conditioning therapy to clinical response, and the promise of CAR T cells directed against additional molecular targets more highly expressed on long-lived plasma cells (eg, BCMA, CD38). Preliminary data in antiphospholipid syndrome indicate the potential of CAR T cells directed against autoantigens.

There are several additional unmet needs regarding the development of effective therapies and clinical trial design. First, it is necessary to define the distinct biological features of disease and response to therapy in SLE males versus females. In addition, there is a need for biomarkers and tools that can be consistently used across clinical research studies and trials. Regulatory agencies must broaden their support for clinical trial designs that incorporate the priorities of the patient community, learnings from research advances and from previous clinical trials, and insights regarding disease pathogenesis. Examples include allowing endpoints reflecting pharmacodynamic/functional outcomes (eg, inhibition of type I interferon pathway activation; inhibition of urine biomarkers). In addition, advances in treatment of lupus patients could be accelerated if the regulatory agencies and/or trial sponsors would make available to the research community its accumulated efficacy, safety and pharmacodynamic data derived from completed lupus clinical trials. Greater crosstalk among regulatory agencies, patients and experts is needed.

Further clinical trial design needs include defining trial designs that will decrease the rate of placebo response. Pregnant women and younger patients (< age 18) must be included in clinical trials. There also remains the need to design clinical trials targeting patients who do not have high disease activity with the goal of addressing significant clinical outcomes (eg, steroid sparing, patient-related outcomes). Select clinical trials should incorporate measures of atherosclerosis (eg, coronary artery CT score) and central nervous system (CNS) disease. Lastly, there is need for specific treatments in refractory antiphospholipid syndrome.

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Systemic sclerosis and vasculitis

Many therapeutic options such as immune modulation using mycophenolate mofetil rituximab and tocilizumab, and the anti-fibrotic nintedanib are available for the treatment of SSc. Great progress has also been made in the application of autologous bone marrow transplantation as treatment for patients with severe SSc. However, it is currently still unclear for which patients and in which setting these therapeutic approaches are most beneficial. Clear guidelines how to use these novel approaches in an individualised and evidence-based way are lacking and studies analysing the risks and benefits for using these approaches in combination, sequentially after non-response, or at early disease stages are needed. Similarly, there is no consensus yet on a standardised protocol for bone marrow transplantation as a treatment for SSc. With more therapeutic agents for SSc being evaluated, including JAK inhibitors or novel approaches such as deep B cell depletion, anti-CD20 antibodies and CD19 directed CAR-T cells, further assessment of how to make best use of these approaches become all the more important.

In general, as with many other IMIDs, there is a lack of biomarkers to stratify patients with SSc for therapies. New opportunities to find biomarkers that predict response or disease progression might lie in the application of cutting-edge technologies such as single cell immunophentoyping, for example, in bronchoalveolar lavage samples.[47]

Consensus is also needed in SSc patient monitoring. Even though first promising steps have been published,[48] clear evidence-based guidelines to determine which parameters should be measured regularly during follow-up examinations and at what intervals follow-up examinations should be scheduled are still lacking. Improved guidelines are in particular needed in the management of SSc lung disease.

To improve outcomes for patients with SSc, it was agreed that early identification and early referral to a specialties centre is important. Close collaboration of general practitioners and rheumatologists with such centres is seen as offering substantial benefit for patient care and disease management. It was noted that there is little understanding of underlying mechanisms and no treatment of calcinosis, gastrointestinal involvement, joint involvement, pain and fatigue. Research is also needed in the area of understanding and treating SSc associated vasculopathies including pulmonary arterial hypertension, digital vasculopathy and renal crisis. Furthermore, there is still a lack of treatment and improved outcome measures for skin fibrosis, even though research in this area has progressed substantially.

Regarding vasculitis, it was discussed that the rarity of these diseases substantially hampers the conduction of research and clinical trials in this field. There was the impression that the progress in other fields in regard to novel treatment option and schemes is not fully translated in the vasculitis field. Building interdisciplinary specialised care centres under the lead of rheumatologists including nephrologists, pneumologists, neurologists, and so on, might help to foster research and to improve patient management, in particular in maintenance therapy. The fast track approach developed for giant cell arteritis (GCA) could be used as role model for such specialised care approaches.

Current therapies, in particular corticosteroids, are associated with life-threating side-effects such as malignancies, cardiovascular events and infections and there is still a lack of understanding why particularly patients with small-vessel vasculitis have high susceptibility to develop hypoimmunoglobulinaemia and high infection rates. Concerns about the high risk for patients to develop infections during immunosuppressive therapy and fears that the response to vaccination will be compromised were aggravated during the COVID pandemic.

In GCA, reduction of cortisol dosage and shortening of time to diagnosis are still unmet needs. Understudied areas in vasculitis research are localised granulomatosis with polyangiitis, which carries a high burden for patients and is difficult to manage for clinicians. Treatment of CNS symptoms is also not adequately addressed yet, and evidence-based recommendations or guidelines for these conditions are lacking.

SUMMARY

The 23rd ATT meeting articulated the major unmet scientific and clinical needs in the field of rheumatology (table 1). Progress has been made with regard to disease endotyping and treatment of early disease, but there still remains a strong need to predict, understand and effectively treat those with refractory disease. The era of precision medicine remains elusive, as we continue to seek molecular signatures that can facilitate more refined targeted treatment and prevention of these immune-mediated inflammatory diseases.

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