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Unmet need in rheumatology: reports from the Targeted Therapies meeting 2019

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ABSTRACT

Objectives To detail the greatest areas of unmet scientific and clinical needs in rheumatology.

Methods The 21st annual international Advances in Targeted Therapies meeting brought together more than 100 leading basic scientists and clinical researchers in rheumatology, immunology, epidemiology, molecular biology and other specialties. During the meeting, breakout sessions were convened, consisting of 5 disease-specific groups with 20–30 experts assigned to each group based on expertise. Specific groups included: rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, systemic lupus erythematosus and other systemic autoimmune rheumatic diseases. In each group, experts were asked to identify unmet clinical and translational research needs in general and then to prioritise and detail the most important specific needs within each disease area.

Results Overarching themes across all disease states included the need to innovate clinical trial design with emphasis on studying patients with refractory disease, the development of trials that take into account disease endotypes and patients with overlapping inflammatory diseases, the need to better understand the prevalence and incidence of inflammatory diseases in developing regions of the world and ultimately to develop therapies that can cure inflammatory autoimmune diseases.

Conclusions Unmet needs for new therapies and trial designs, particularly for those with treatment refractory disease, remain a top priority in rheumatology.

BACKGROUND

The Advances in Targeted Therapies meeting (ATT) has met annually for 21 years, bringing together clinical scientists and immunology and molecular biology experts from around the world. The meeting focuses on clinical and translational research, in immune-mediated inflammatory diseases (IMIDs) and stimulates collaboration between basic scientists and clinicians. The meeting's objective is to update participants regarding the latest insights regarding disease mechanism(s) and pathophysiology and recent developments with both existing and novel targeted therapies in the field of IMIDs with a focus on rheumatological diseases. Previously, a consensus document describing the recommended use of targeted therapies within rheumatology was produced from this meeting.¹ However, with the expanse of targeted therapies and the recent clinical recommendations

Key messages

What is already known about this subject?

- ▶ Key unmet needs in field of rheumatology clinical and basic science research have been highlighted previously, but vary over time as the field progresses.

What does this study add?

- ▶ The Advances in Targeted Therapies meeting (ATT) focuses on clinical and translational research, in immune-mediated inflammatory diseases (IMIDs) and stimulates collaboration between basic scientists and clinicians. With the 2019 meeting, we reviewed, updated and prioritised the unmet research needs in the field
- ▶ This effort highlighted several overarching themes: the need to innovate clinical trial design with emphasis on studying patients with refractory disease, the development of trials that take into account disease endotypes and patients with overlapping inflammatory diseases, and the need to better understand the prevalence and incidence of inflammatory diseases in developing regions of the world.

How might this impact on clinical practice?

- ▶ The prioritisation and highlighting of research needs, particularly in aspects of clinical trial design, will ultimately result in improvements in therapy and potentially the better targeting of therapies toward patients with specific disease sub-types.

published from both American College of Rheumatology and the European Union League Against Rheumatism,^{2–4} a document covering all targeted therapies across all disease indications became too complex and voluminous as a single manuscript. Accordingly, the annual meeting's output was modified to discuss key unmet needs within the field, consistent with the meeting's underlying objective of promoting innovation and collaboration.⁵ With the 2019 meeting, we conducted a similar process to review and update these unmet needs, but in this case, prioritise and highlight the most important needs in the field.



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METHODS

We assigned conference participants to disease-specific breakout groups which included psoriatic arthritis (PsA), rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), systemic lupus erythematosus (SLE) and other systemic autoimmune rheumatic diseases including vasculitis. Experts in each group were tasked with identifying unmet needs in three categorical areas: clinical care, clinical science and therapeutic development and basic/translational science. A ‘facilitator’ and ‘rapporteur’ led each group’s discussion and summarised their results, and the groups were asked to highlight notable progress made towards previously identified needs as well as identify new areas of need. This year, each group was asked to then prioritise their discussion and detail the top several needs within each disease-specific area.

RESULTS

Rheumatoid arthritis

There was broad agreement that management of patients with RA who are refractory to available treatments (‘refractory’ or ‘treatment resistant’ RA) is arguably the greatest unmet need in RA (at least in the developed world). However, a careful clinical definition of the refractory state is needed, so that we are not confounding true treatment-refractory disease with patients with RA who are undertreated, non-adherent to treatment or who have comorbid fibromyalgia or other sources of non-inflammatory pain. Once a clinical definition of ‘refractory’ RA is achieved, a molecular definition of the refractory state should follow and should be differentiated from molecular definitions of early RA, established RA, RA in flare and RA in remission. Single cell analysis of synovial and/or circulating cells (including gene expression) may enable us to phenotype RA into subgroups or states of disease.⁶ Molecular characteristics at single cell level should be compared with whole synovial tissue molecular profiling with the aim of identifying peripheral blood surrogates of tissue pathology (liquid biopsy) and treatment response. The definitions of molecular subgroups could eventually lead to a personalised approach to treatment. For example, data generated may suggest that a combination or sequence of biologics may be efficacious in some individuals. Alternatively, molecular subgrouping may identify novel targets proximal in the disease process—that is, in the early adaptive immune response—that could be targeted for drug development and clinical trials.

Importantly, patients who have received multiple biologics/small molecules should not be excluded from clinical trials since they have the greatest unmet need. Novel targeted therapies should be studied in refractory patients, as should novel combinations or sequences of existing therapies, similar to the way oncologists use checkpoint inhibitors. In particular, we should carefully move forward with combination therapy studies in refractory patients, with a commitment to resolving issues of cost, safety (eg, infection and malignancy) and the reluctance of manufacturers to combine each other’s agents. Efforts to identify optimal dosing and levels of our currently available therapies, as a single treatment or in combination, are also essential to optimise treatment of refractory patients. Finally, it is important to recognise that despite many successful therapies for RA, less than half of patients with RA are in remission, 10%–15% are refractory, and there is still no cure for this disease.^{7–9} Continued commitment on the part of our funding agencies, pharmaceutical partners and scientific investigators is essential to advance research and discovery efforts to understanding the heterogeneity of RA pathogenesis and effective sustainable treatments.

Psoriatic arthritis

In the last few years, there have been an increasing number of medications with different mechanisms of action which have shown benefit in PsA in randomised clinical trials and have been approved by regulatory agencies, including an IL12-23 inhibitor (ustekinumab), two IL-17A inhibitors (secukinumab and ixekizumab), an oral PDE4 inhibitor (apremilast), an oral JAK inhibitor (tofacitinib) and abatacept.^{10–11} While very gratifying, the homogeneity imposed by clinical trial design may exclude important patient subgroups. For example, the great majority of patients have polyarticular involvement (entry criteria: ≥ 3 –5 inflamed joints) with few studies examining oligoarticular disease (< 5 inflamed joints); thus, the common oligoarticular PsA represents an unmet need in PsA trials. Although the varied clinical domains of PsA, (eg, enthesitis, dactylitis, spondylitis) can show response to treatment, only a subset of patients demonstrate these domains and thus the measured response may not achieve statistical significance if the subset is too small. Furthermore, a domain such as PsA spondylitis, with symptomatic inflammatory back pain in about 15% and asymptomatic sacroiliitis in about 30% of patients,¹² is not measured by the standards of axSpA trials, including centrally read MRI. The best way to measure oligoarticular disease in trials remains an unmet need, and since the oligoarticular phenotype is a common presentation in clinical practice, we are not able to entirely accurately extrapolate results from trials to clinical practice. For treatment of the spondylitis component of PsA, we rely on data from axSpA trials, which also may not be accurately extrapolatable. Trials of the IL-12/23 inhibitor ustekinumab and the IL-23 inhibitor risankizumab have failed in ankylosing spondylitis.¹³ Even though these agents have demonstrated benefit and been approved for PsA, their ability to benefit the spinal component of PsA remains unproven and needs to be tested.

Phase IIIB or IV trials which specifically enrich the patient population for the domain or subtype in question are needed. Enrolment criteria could require oligoarticular disease or spondylitis or enthesitis for example, although measurement techniques for these disease aspects still need to be developed. Specific ultrasound or MRI (eg, axial clinical and imaging measures for a spondylitis-specific trial, enthesal-specific measures and imaging for an enthesitis trial) are needed. It is not clear how the results of these trials could be incorporated into regulatory labelling for the medication, but these would provide important clinical data helpful for clinical decision-making.

A second area of major unmet need in PsA is management of the therapy refractory patients who have ‘tried everything’. Emergence of new approved therapies will partially address this need, as would rational ‘combination’ studies. Clinicians are more frequently trying unapproved combination approaches, for example combining a biological medication (TNFi, IL-17i and so on) with an oral agent such as a PDE4i or JAKi. Combination therapy trials are urgently needed, although the safety of such combination approaches is unknown, particularly with regard to infection, where a greater risk has been suggested in some combination trials for RA.¹⁴

A third major area of unmet need is better understanding of, and accounting for, the role of central sensitisation (CSS) (chronic widespread pain, fibromyalgia) in amplifying symptom severity. Recent studies have demonstrated that 15%–40% of patients with PsA and other rheumatic, chronic pain and inflammatory conditions may have concomitant CSS. When CSS is concomitantly present with PsA, disease activity measures which include patient-reported outcomes, (eg, pain, patient global)

are nearly twice as severe when compared with a similar PsA cohort that lacks CSS.^{15–17} Patients with PsA with concomitant CSS are less likely or unable to achieve targets of treatment such as minimal disease activity,^{16–18} Højgaard *et al* demonstrated in this population lack of correlation between tender enthesal examination and evidence of objective evidence of inflammation by ultrasound.^{17 18} While patients with CSS are historically excluded from PsA trials, it is difficult to exclude all such patients. Several measures have been developed to ascertain the presence of CSS/fibromyalgia;¹⁷ however, there remains a need for more objective biomarkers which are more feasible to use in clinical and trial settings. In this respect it is noteworthy, that the treat-to-target recommendations for PsA explicitly state that ‘The choice of the target and of the disease activity measure should take comorbidities, patient factors and drug-related risks into account’ (recommendation #8);¹⁹ this simply means that an index developed for measuring disease activity in PsA should not be used to score a comorbid condition, alternatives will then have to be used. Similarly, a prerequisite for application of classification criteria for RA is that a patient has no other diagnosis, such as SLE.²⁰

Ankylosing spondyloarthritis

In 2018, the spondyloarthritis discussion group identified a variety of unmet needs which included: understanding the relationship of peripheral disease to axial disease; early recognition and diagnosis of disease; understanding the causes/relationship of extra-articular disease including bowel and eye disease to the joint disease; improved imaging technologies and interpretation; development of biomarkers for prognosis and choice of therapy; a wider choice of biological therapies; an ability to improve prognosis (disease modifying treatment); direct comparison among TNF inhibitors with regard to efficacy and safety; more frequent disease remission; improved referral to a rheumatologist and international collaboration.²¹

Although this list is comprehensive, additional themes were identified as most important. First, the need to better understand the microbiome is paramount. While it is highly likely that the gut microbiome is contributing to the disease, we do not know which bacteria are most important, which portion of the bowel is most important, the mechanism by which the bacteria affect the disease, the role of non-gut microbiota, the role of non-bacterial microbiota or how best to therapeutically alter the gut microbiome as by diet or faecal transplant. Second, the failure to establish IL-23 as an effective therapeutic target in ankylosing spondylitis means that we need to understand more completely the IL-23-IL-17 axis and the role of IL-23 and additional cytokines in the molecular pathogenesis of this disease.^{22–25} This effort should include a more complete understanding of the relative function of all members of the IL-17 family, including IL-17F and further understanding of which cells secrete IL-17 and why this does not seem to be under the control of IL-23 in this disease.²⁶ We also need a better understanding as to how the disease results in both new bone formation and osteoporosis.²⁷ Unfortunately, it still takes many years in daily clinical practice before a diagnosis of axial SpA is made.^{28 29} Therefore, approaches for referral in primary care and for early diagnosis have to be further developed and implemented. Last, there is still further need for international agreement (and implementation) on nomenclature of axial SpA.^{30 31}

Systemic lupus erythematosus

Recent failures of clinical trials in SLE demonstrate weaknesses in current methodology and opportunities for improvement in

multiple areas.^{32–37} The theme of improving clinical trial design, including limiting disease heterogeneity, was prioritised in discussion. Specifically, learning from already available data was deemed essential. Analysis of the primary data from completed clinical trials, especially combining those from several studies, can provide essential insights that can guide decisions for new studies.³⁸ Comparing the characteristics of the patients that participated in the trials with the data that are available from independent patient registries could be helpful to identify a bias in trial patient selection that might help to better understand trial outcomes. Issues that may confound clinical trials, including which patients should, or perhaps more importantly, should not be enrolled can be addressed using this type of analysis. Furthermore, evaluation of potential outcome measures^{39–41} and the effects of background therapy or comorbidities that impact relative response to the study drug can be determined. This type of analysis has limitations related to which patients were actually enrolled in the trials to be analysed. Here, an appropriate serological test to identify autoantibody positive patients based on sound technology is paramount.^{42 43} Other datasets that may inform clinical trial design in different ways include patient registry studies, electronic medical record cohorts and administrative datasets, although issues of data quality, completeness and timeliness must be considered.^{44–47} Lupus trials are typically conducted with background therapy^{32 35 48 49} and there is little agreement on how this should be controlled during the conduct and analysis of a study.⁴³ In fact, the ‘standard of care’ medication in SLE in general has not been defined.^{43 50}

There are important ongoing issues surrounding the disease heterogeneity that also affect clinical trial design.⁴³ With respect to inclusion criteria, targeting a single organ or specific subgroup could lead to more definitive conclusions regarding a study drug.⁵¹ The marked variability in disease severity of enrolled participants could also impact the ability to draw conclusions.⁵² For example, including participants with low disease activity could introduce floor effects that limit the ability to separate placebo from active treatment. On the other hand, patients with the greatest need of novel treatment approaches, namely with life threatening disease,⁵³ are usually excluded from clinical trials. The impact of disease duration and previous treatment on the study population may also influence the effect of a study drug. The selected outcome measures can substantially influence whether a clinical trial meets its intended endpoint. New potential outcome measures have been proposed, such as the SLE-disease activity score,⁵⁴ intended as a continuous variable and the Lupus Low Disease Activity State.⁵⁵ Another outcome measure, LuMOS, was developed from analysis of the belimumab trials and shows superior ability to detect change compared with the standard SRI-4.³⁸ Other potentially novel outcome variables for this heterogeneous disease might include hierarchical outcomes. Using biomarkers either for inclusion or outcome may solve issues surrounding disease heterogeneity.

Novel trial designs that could be used for SLE include adaptive designs currently used in oncology.⁵⁶ Drug withdrawal trials⁵⁷ or trials that use flare for inclusion or outcome could also be considered as they allow the participation of patients with more severe disease. Novel designs might focus on reducing the impact of placebo response, including placebo response related to pretrial non-compliance.^{58 59} In considering targets of treatment, it is tempting to focus on autoimmune inflammatory manifestations where exciting new discoveries provide novel targets.⁶⁰ However, it is essential to include patient-focused unmet needs.^{61 62} These include symptoms that impact quality of

life such as pain, fatigue and cognitive dysfunction ('lupus fog') which are typically resistant to immune-focused therapies. Treatments that could improve medication adherence, especially in socially deprived populations and by approaches which require less frequent dosing, or that can mitigate the important concern of reproductive issues, are needed. Overall, there are abundant opportunities for clinical scientists, pharmaceutical companies and regulatory bodies to collaborate towards improved methodology to provide better patient outcomes.

Other systemic autoimmune rheumatic diseases

This group highlighted the unmet needs primarily within systemic sclerosis this year, and similar to other groups, identified the issue of improving clinical trials of utmost importance. Recent and current clinical trials have failed to demonstrate efficacy for a variety of agents in the treatment of this disease, although the results suggest that some disease manifestations may actually be improved by certain agents.⁶³ One difficulty in designing clinical trials to date has been the heterogeneity of disease manifestations. It might be appropriate to design trials for a specific manifestation for example (eg, lung disease). Alternatively an acceptable, sensitive, specific and quantitative combined outcome measure that would be acceptable to regulatory agencies could speed the design and development of trials for registration of new therapeutic agents.⁶⁴ A dearth of predictive biomarkers also makes it difficult to target drug trials to those with the greatest potential for benefit from specific therapeutic interventions.^{65 66} Finally, inclusion of patient-reported outcomes of specific manifestations (eg, calcinosis) could allay patients' concerns about entering trials.⁶⁷

Table 1 Identified unmet research needs of high priority within RA, PSA, AxSpa, SLE and other systemic autoimmune rheumatic diseases

Rheumatoid arthritis	The need to better define treatment 'refractory' states both phenotypically and molecularly
	The need to focus on refractory patients in both the study of novel targeted therapies and in the study of existing therapies in novel combinations or sequences
Psoriatic arthritis	Understanding differential therapeutic effects on different clinical domains in PsA such as enthesitis
	Further evaluation of combination therapies and strategic trials including the use of sequential therapies, controlled withdrawal, the treatment of early disease and the treatment of monoarticular or oligoarticular disease
Ankylosing spondyloarthritis	Understanding the role of the microbiome in disease pathogenesis and potential therapy
	Understanding disease pathology specifically with regard to why IL-23 inhibition does not improve the disease.
Systemic lupus erythematosus	Improving clinical trial design by reducing heterogeneity of participants, developing new outcome disease activity measures, standardising serological testing and conducting organ-specific trials
	Consider alternative trial designs including adaptive trials and withdrawal trials
Other systemic autoimmune rheumatic diseases	Improving clinical trial design, specifically with reducing heterogeneity in disease endotypes and the use of organ-specific outcome measures
	Identification of predictive biomarkers and the inclusion of patient-reported outcomes of specific manifestations (eg, calcinosis) for clinical trials

axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

SUMMARY

The convening of the 21st ATT afforded the possibility to discuss and articulate major unmet needs in the field of rheumatology, and across domains there were several overarching perceived unmet needs (table 1). It was generally understood that there has not been sufficient emphasis on trial designs which concentrated on well-defined disease subtypes. Many diseases have multiple subtypes (eg, axial and peripheral PsA or limited/diffuse systemic sclerosis with multiple serological subtypes) and trial designs which mix those subtypes could obscure the success of treatments in specific subgroups. Likewise, trial designs which are able to dissect (or include) overlapping diseases are also needed.

While there has been some success in treating moderate to severe patients with various inflammatory rheumatic diseases and even inclusion of some patients with Disease Modifying anti-Rheumatic Drugs (DMARD)-refractory disease in RA, this remains a top unmet need in RA that has been even less carefully examined in patients with other diseases. For example, patients with PsA are often included in trials only if they have been naïve to previous conventional synthetic DMARD (csDMARDs) or biologic DMARD (bDMARDs); more attention needs to be paid to patients who are more 'difficult-to-treat' across all conditions, as well as those who have multiple complications or comorbidities or those who have failed other csDMARDs or bDMARDs.

Last, while progress has been made in treating patients who used to have unmet need within countries and regions such as Australia, Japan, North America and the European Union, it was highlighted that more emphasis needed to be placed on understanding unmet needs in other countries and continents such as Africa, multiple areas in Asia and Central and South America.

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