Precision Medicine in Systemic Lupus Erythematosus

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A session on precision medicine in systemic lupus erythematosus (SLE) took place at the European Alliance of Associations for Rheumatology (EULAR) 2023 meeting in Milan, Italy, merging one of the most contemporary topics in modern healthcare with an important subject in the rheumatology specialty. Co-chaired by Dimitrios Boumpas, University of Athens, Greece, and José Pego-Reigosa, University Hospital Complex of Vigo, Spain, this series of presentations was among the most highly attended, and featured cutting-edge insights from front-running experts on lupus.

MOLECULAR MECHANISMS AND HETEROGENEITY

Spotlighting heterogeneity, unpredictability, and difficulties with early diagnosis, Marta Alarcón-Riquelme, Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research (GENYO), Spain, drew attention to the three pillars healthcare professionals face in precision medicine for SLE and other autoimmune diseases. Alarcón-Riquelme exhibited the research that they have led on reclassifying systemic autoimmune diseases, regardless of their clinical diagnosis. This utilised PRECISESADS, a study that has gathered data on SLE, amongst other autoimmune conditions, such as rheumatoid arthritis, Sjögren's syndrome, and systemic sclerosis.

Using molecular patterns to predict flares or long-term remission is an avenue that shows promise; findings have shown that the speed of reduction in dysregulation of some gene expression modules using neutrophils, platelets, plasma cells, and erythrocyte modules can predict long-term remission. Alarcón-Riquelme noted that interferons are not good predictors of remission due to their slow rates of disappearance, but explained that close to a flare, there is a high probability of finding platelet and erythrocyte modules, and this can be used to forecast, thus tackling unpredictability.

This research also investigated which types of cells differentiate patients belonging to separate transcriptome groups, and how these differ on a single cell level when responding or not responding to therapy.

Alarcón-Riquelme went on to discuss the European 3TR project, which they currently co-ordinate. It examines the mechanisms of known response to treatment across multiple diseases, including SLE. The question that this research aims to answer is if molecular patterns can predict therapeutic responses and mechanisms of no response across these diseases, which would improve diagnosis and further our understanding.

Next steps in this field involve identifying molecular patterns of response and non-response, identifying protein markers for drugs that follow the behaviour of these molecular patterns, and how to directly translate applications of these patterns into clinical practice.

CLASSIFICATION AND DIAGNOSIS

Martin Aringer, University Medical Center Carl Gustav Carus, Technische Universität Dresden, Germany, began by highlighting the requirement for high specificity when defining classification criteria.

Aringer presented the EULAR/American College of Rheumatology (ACR) criteria for SLE and highlighted differences when compared with other systems, such as with using antinuclear antibodies as an entry criterion. "Lupus is not a particularly uniform disease, and that is one of the challenges we face," was the way Aringer described the variability and complexity of lupus as a condition, which harbours difficulties with classification and diagnosis. A barrier to consider when looking at translating these parameters into practice is feasibility, which can be an issue when deciding on what criteria that will work worldwide; it is because of this that some criteria have been left out at this stage.

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Turning to molecular stratification, Aringer explained that distinct differences, from a clinical point of view, allow classification into subsets of SLE as a disease entity and guide therapy selection for patients. However, these groups are not specific enough to clarify between diseases at present. Using graphs to compare SLE and Sjögren's syndrome, an area that is always difficult to classify, Aringer highlighted overlaps in molecular group measurements, and reassured the audience that there are ways to differentiate, such as comparing interferons. The information from this presentation demonstrated that molecular grading is good and improving, but clinical diagnosis is still better at present, and moving forward, these branches should be used in conjunction.

Concluding, Aringer emphasised the complexity and one of the main challenges associated with the precision approach to lupus classification and diagnosis, stating that any patient with lupus "may have any symptom combined with any other; there is not a fixed combination."

IDENTIFYING THE RIGHT THERAPY

Acknowledging that there is a growing problem in choosing between all the available therapies with different mechanisms of action, Edward Vital, University of Leeds, UK, focused on drugs that are close to being in the clinic, or are already there. Beginning by comparing selection of belimumab and anifrolumab for non-renal SLE, Vital discussed the usefulness of existing biomarkers in a precision approach for existing therapies.

Vital provided three ways in which biomarkers are helpful in stratifying SLE trials: identifying individuals with active disease, predicting flares and remissions, and highlighting the presence of immune endotypes. Plasmablasts were one of the biomarkers under question; not directly killed by rituximab, and with a short lifespan in circulation, it is a possible indicator of B cell activity at other sites. Shifting to discuss rituximab, Vital explained that "one of the issues with rituximab is that it does not deplete B cells as well as we initially thought." This presentation clarified that complete B cell and plasmablast depletion predicts better clearance of autoantibodies and clinical response for therapies, a helpful idea to guide future precision approaches. Vital described the effectiveness of new Type 2 monoclonal antibodies killing B cells directly, providing better B cell depletion, and touched on the promising emergence of chimeric antigen receptor-T mechanisms that reprogramme a patient's T cells to target B cells.

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Delving deeper into precision initiatives for SLE, Vital questioned if killing B cells more intensively is the correct approach. Although B cell depleting therapies are useful for physicians and patients, patterns of relapse have been found dependent on the proportion of returning plasmablasts.

"It seems to me this is not a function of how well the B cells were killed in the first place; rather, it is a function of the immune environment into which they return," was the explanation Vital provided, simplifying things to: "Lupus is in the soil."

Presenting a problematic case of cryoglobulinaemia from their own clinic, Vital concluded by describing a successful approach that targeted plasma cells directly ahead of B cells, resulting in complete remission with no further therapy 8 years on. This plasma targeting mechanism is undoubtedly an important option for patients with B cell-independent and antibody-dependent disease.

Coming full circle, Vital provided advice for physicians struggling with therapy selection, and described the case that first sparked their interest in lupus, involving interferon activity that results in antiviral and immunostimulatory responses. Vital emphasised the complex processes involved in lupus, and praised innate immune targeting as a different way of conducting treatment.

CONCLUDING REMARKS

Rounding off the session, Sarah Dyball, University of Manchester, UK, presented the classification criteria for clinical trials as treatment becomes more precise. Dyball warned that a large proportion of patients are excluded from Phase III trials as they do not meet eligible clinical diagnosis or fulfil criteria for an overlap syndrome. New criteria may take several years to be adopted into practice, and Dyball recommended a shift away from classification criteria, instead moving towards a stratified approach using immunopathology, such as molecular stratified basket trials for connective tissue disease.

A consistent theme throughout the session was the great complexity of SLE. Insights provided by the speakers in this session will impact the decision-making of clinicians and guide future research, in turn contributing to further unravelling this intricate and perplexing disease, and resulting in more accurate targeting of precision medicine. ●

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