Difficult-to-Treat Disease in Rheumatology

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Citation: EMJ Rheumatol. 2023; DOI/10.33590/emjrheumatol/10303934. https://doi.org/10.33590/emjrheumatol/10303934.

THE CHALLENGE of difficult-to-treat disease in rheumatology was explored during an insightful clinical science session at the European Alliance of Associations for Rheumatology (EULAR) 2023 Congress, which took place in Milan, Italy, between the 31st May–3rd June. The session, entitled 'Everything is difficult to treat?', explored key elements that contribute to the challenge in treating rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc).

INTRODUCTION

The session was chaired by Jacob M. van Laar, University Medical Center Utrecht, the Netherlands, and László Czirják, Medical School, University of Pécs, Hungary. Whilst the experts discussed different rheumatological conditions, they highlighted several recurring themes, as well as disease-specific challenges that contribute to treatment difficulty.

DEFINING 'DIFFICULT-TO-TREAT'

Defining 'difficult-to-treat' across these four conditions is challenging. There are some cross-applicable characteristics alongside disease-specific features. This, compounded by challenges in accurate or delayed diagnosis, can muddy the water in terms of defining if a disease is in fact difficult-to-treat or not.

György Nagy, Semmelweis University, Budapest, Hungary, discussed the EULAR definition for difficult-to-treat RA, which is based upon three criteria. The first criterion is failure of ≥2 biologic/targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARD) with different mechanisms of action, after failing treatment with conventional synthetic (cs) DMARD therapy (unless contraindicated).

The second is the presence of signs suggestive of active or progressive disease, defined as ≥1 of the following: at least moderate disease activity according to validated composite measures, such as DAS28-ESR >3.2 or CDAI >10; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment to <7.5 mg/day of prednisone or equivalent; rapid radiographic progression, with or without signs of active disease; and RA symptoms causing a reduction in quality of life. The third and final criterion is the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or patient.

In the absence of a specific definition for axSpA, SSc, or SLE, Mariusz Korkosz, Jagiellonian University Medical College and University Hospital, Kraków, Poland, explored whether the EULAR definition for RA can be applied to axSpA. Criteria one and three can be extrapolated to apply to axSpA, Korkosz confirmed. However, criterion two requires adjustments to be applicable. Rapid radiographic progression is not applicable to axSpA, and the inabilityto taper glucocorticoid treatment would need to be changed to the inability to reduce or discontinue non-steroidal anti-inflammatory medication.

WHAT MAKES THESE CONDITIONS DIFFICULT TO TREAT?

Common themes, including comorbidities, treatment failure, and treatment adherence were, discussed across the expert presentations.

David Isenberg, University College London, UK, highlighted that whilst survival has improved, 15% of patients with SLE die within 15 years of diagnosis. Isenberg explored the four key factors that make SLE a difficult disease to treat.

Firstly, Isenberg stated: "Lupus is truly the great mimic," and showcased the numerous ways in which lupus can manifest. This clinical heterogeneity, in turn, can impair the ability to make the diagnosis quickly, and without accurate diagnosis the appropriate treatment will inevitably be delayed.

Furthermore, Isenberg explained that SLE is unpredictable, and whilst there are three distinct patterns of disease, these do not cover disease trajectories in all patients, and only 15% of patients achieve complete remission. Isenberg also commented that limitations of current therapeutics also contribute to the difficulty in treating SLE.

In relation to the latter, Isenberg discussed how the options available to treat SLE after conventional treatment failure are limited, which is not the case for other rheumatological conditions. However, they did express hope for the future with new biologics in development, and the potential role for chimeric antigen receptor (CAR) T-cell therapy.

Additionally, Isenberg discussed comorbidities as a factor in difficult-to-treat disease. Up to 30–40% of patients with lupus will have other autoimmune disease diagnoses. Such comorbidities add to the complexity of disease management, thus contributing to treatment difficulty. Other scenarios that pose treatment difficulty, including aggressive lupus nephritis, lupus psychosis, SLE plus anti-phospholipid syndrome, and SLE plus infection, were also considered in further detail.

Comorbidities were also discussed in the other expert presentations. Nagy commented that 10% of patients with RA are difficult to treat in clinical practice, and explored the factors associated with difficult-to-treat RA, highlighting comorbidities, behavioural and lifestyle factors, rapid radiographic progression, and disease refractory to glucocorticoid and/or DMARD therapy as key contributors.

Nagy also explored the role of pain and inflammation in difficult-to-treat RA, highlighting a study assessing the relationship between pain and inflammation in difficult-to-treat disease compared with healthy controls. Preliminary data from this study have shown that right and left postcentral gyrus connectivity

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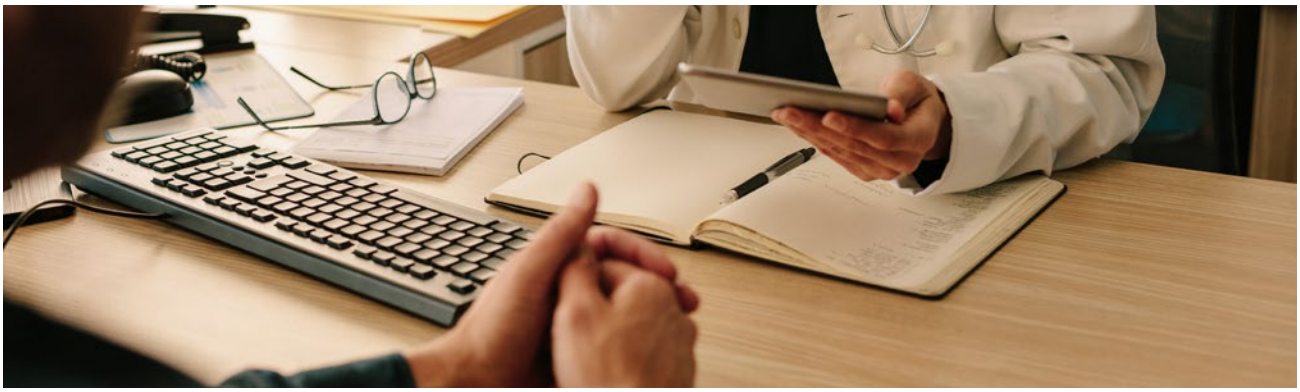

strength drops following pain stimuli in patients with difficult-to-treat disease, compared to no change in connectivity in healthy controls, Nagy explained. This data was statistically significant and reproducible. However, further work is required to elucidate these pathways further, and investigate their potential in managing difficult-to-treat RA.

In terms of axSpA, Korkosz also highlighted comorbidities as a characterising feature for difficult-to-treat disease. Alongside this, it was explained that extra-musculoskeletal and peripheral disease manifestations, clinical heterogeneity, structural damage, and patient expectations also play a role in difficult-to-treat disease.

Regarding SSc, Gabriella Szücs, University of Debrecen, Hungary, highlighted complex pathogenesis; lack of gold standard for assessment of disease activity, which makes it difficult to identify those at risk of early progression; and, in agreement with Isenberg, commented how diagnostic delays, clinical heterogeneity, and limited treatment options contribute to the difficulty in treating the disease. Szücs explained how the different potential organ manifestations of SSc mean that there is no single treatment strategy that can be applied to patients with SSc. They further discussed how several of these organ manifestations are very difficult to treat, spotlighting interstitial lung disease, pulmonary arterial hypertension, digital vasculopathy, calcinosis, gastrointestinal symptoms, and cardiac disease.

FUTURE DIRECTIONS FOR DIFFICULT-TO-TREAT DISEASE

When exploring ideas for future directions, the experts discussed the importance of prognostic factors in predicting difficult-to-treat disease; the need for translational research and clinical trials to optimise new therapeutics and therapeutic targets; the potential role of artificial intelligence to develop predictive algorithms; developing disease-specific definitions and guidance for difficult-to-treat disease; and for SLE specifically, the potential for, and outcomes of, studies investigating the use of CAR T-cell therapy.

CONCLUSION

Difficult-to-treat disease is complex, and management requires the consideration of several contributing factors that are both patient- and non-patient related. The approach to management should be multifactorial, and involve a combination of pharmacological and non-pharmacological strategies. Working towards improved time to and accuracy of diagnosis, risk prediction, and optimisation of comorbidities are key challenges involved in the management of difficult-to-treat disease. Future efforts should focus on translational research and clinical trials, novel therapeutic options, personalised treatment pathways, and the development of clear definitions and guidelines to aid clinicians in the management of difficult-to-treat rheumatological diseases.

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