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Progressive Multiple Sclerosis: Time to Trial Something New?

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PROGRESSIVE multiple sclerosis (MS) posed an important topic of discussion at the 38th European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress, held in Amsterdam, the Netherlands, between 26th–28th October 2022. Throughout the engaging session on progressive MS, chaired by Kathy Smith, National Multiple Sclerosis Society, New York, USA, and Jan Meilof, University of Groningen, the Netherlands, key learning and focus points to consider for the future of clinical trials and treatments were summarised and spotlighted.

CURRENT PROGRESSIVE MULTIPLE SCLEROSIS CLINICAL TRIAL DESIGNS: WHAT ARE THE ISSUES?

Ruth Ann Marrie, University of Manitoba, Winnipeg, Canada, delivered an insightful presentation that reflected upon how the patient perspective is inadequately considered in progressive MS trials, and further emphasised that measures representing the impact on activities of daily living are needed to obtain a full picture of how progressive MS impacts those living with the disease.

Marrie highlighted that, in terms of clinician-assessed outcome measures, a study by McAdams et al.[1] revealed that out of 17 Phase III clinical trials performed in secondary progressive MS, 16 included the Expanded Disability Status Scale (EDSS) as the outcome measure. Although this is a familiar measure that is relevant to patient function, it relies on clinician neurological examination, which is not standardised, and it also relies heavily on the assessment of lower limb motor function. It is relatively insensitive to other features of progressive MS such as cognitive, visual, and upper limb motor function. This lack of holistic assessment poses a problem for identifying effective therapies targeting all aspects (motor, sensory, and cognitive) of the disease.

Even though 40–70% of people with MS have cognitive impairment and cognitive preservation is of high importance to both clinicians and patients, there is inadequate assessment of this as an outcome measure in clinical trials. McAdams et al.[1] found that only six out of the 17 Phase III trials that were included in their analysis assessed cognition. Marrie further stated that when cognition was assessed, only a single test was used, which "in a complex construct like cognition" is insufficient.

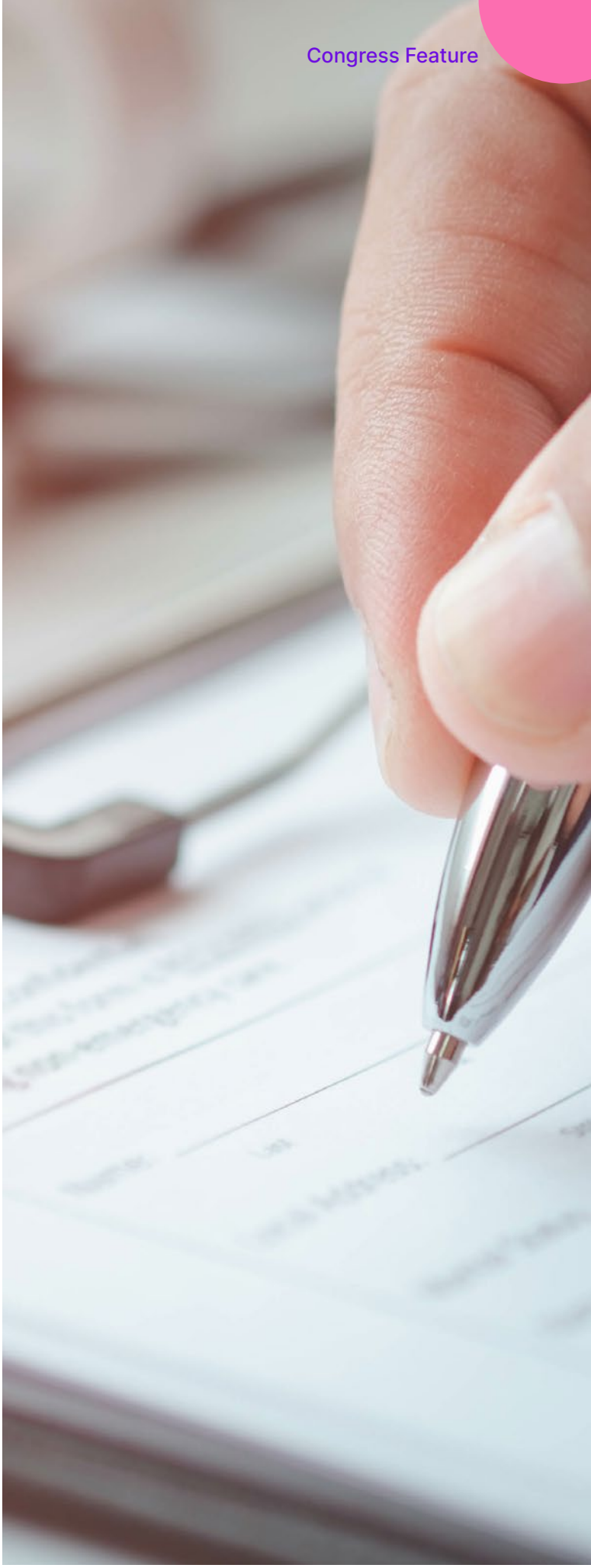
When considering the use of patient-reported outcome measures in clinical trials, one of the main relevant psychometric properties is responsiveness; however, Marrie highlighted that there is limited information on the responsiveness of tools used for patient-reported outcome

measures in clinical trials for progressive MS. In addition to this, it was noted that there is a lack of validated patient-reported outcome measures for all aspects of MS. A study by Marrie and colleagues[2] demonstrated that the health utilities index 3, a patient-reported outcome measure with strong psychometric properties for MS was more efficient in detecting change in disability and employment status than other measures such as the RAND-12. Marrie discussed how this should therefore be considered when selecting outcome measures for progressive MS clinical trials.

Maria Pia Sormani, Department of Health Sciences, University of Genoa, Italy, and IRCCS Policlinico, San Martino, Genoa, Italy, explored clinical trial designs in progressive MS, focusing on adaptive clinical trials, registry-based randomised controlled trials (RCT), and a proposal regarding innovative approaches to personalised clinical trials. Sormani commented that up until now "we have tested for progressive trials mainly drugs that were already approved for relapsing-remitting MS with very disappointing results," and highlighted that these drugs have had little treatment effect on disability progression. Sormani highlighted how one of the main issues with standard Phase II and III clinical progressive MS trials is the length of study duration, and discussed the need to test different drugs within shorter time frames. However, despite extensive mechanistic research, optimal Phase II outcomes for drugs with different mechanisms of action have not yet been clarified. Sormani commented that identifying how these mechanisms can be targeted as an outcome measure will be a challenge.

HOW CAN WE OVERCOME THE CURRENT CONCERNS?

Marrie discussed the use of composite outcome measures to improve



progressive MS clinical trials, featuring results from a study by Chang et al.[3] In this study, the authors combined several endpoint outcome measures into a proposed composite Overall Disability Response Score (ORDS).[3] They found that using this composite measure made a difference in treatment outcomes between treated and non-treated groups. However, Marrie commented that the use of ORDS as a composite outcome measure requires further validation, and that the results obtained when using these types of outcome measures can be harder to interpret and may not be inclusive of all relevant outcome measures. For example, the ORDS composite in the study by Chang et al.[3] did not include measures for vision or cognition. Additionally, Sormani added that one of the main advantages of using composite outcome measures is being able to perform a trial with a smaller sample size over a shorter time period.

Marrie noted that performance-based outcome measures assessing motor, cognitive, and visual function could be used to complete a more holistic evaluation. A study by Koch et al.[4] showed that disease improvements were seen more often when EDSS was used as an outcome measure when compared to using performance-based outcome measures such as the Timed 25-Foot Walk (T25-FW) test or Nine-Hole Peg Test (9HPT), which were better at identifying disease progression.[4] Marrie highlighted how these performance-based measures were "less noisy," but their interpretation requires conversion to z-scores, which are often "not intuitively understood by clinicians or patients."

One of the outcome measures trials could incorporate to obtain a better understanding of the disease impact on patients is to use patient-reported outcome measures. Sarah Knowles, UK MS Register, Swansea University, UK, discussed a study that utilised the physical Multiple Sclerosis Impact Scale (MSIS-29-Phys), a patient-reported measure of disability and time to significant worsening in disability level, measured by a 10-point increase in MSIS. The use of this outcome measure showed that from onset of disease, disability worsened faster in individuals with late-onset MS and a relapsing-remitting disease course, but not those with a progressive disease course. Knowles commented that this highlighted how late-onset patients could be a useful population when trialling drugs targeting neurodegeneration, and concluded that the study showed how longitudinal data can be used to enhance clinical trials by identifying suitable participants.

"There is a need for validated patient-reported outcome measures for all aspects of MS that have good psychometric properties, match the intervention of interest, are applicable cross-culturally, and can be measured consistently."

In addition to this, Marrie highlighted how there is a need for validated patient-reported outcome measures for all aspects of MS that have good psychometric properties, match the intervention of interest, are applicable cross-culturally, and can be measured consistently to enable comparison of findings.

When considering how to improve clinical trial design, Sormani discussed the pros and cons for adaptive trials and registry-based RCTs, summarising that the benefits of adaptive trials include flexibility as they do not need to be fully specified at the design stage, which is beneficial when pre-existing

data are limited; provision of higher power for any given sample size, which increases efficiency; and potential harm reduction as ineffective treatments are discontinued at the interim analysis. However, Sormani suggested that implementing adaptive trial designs will be challenging because they take longer to design, require an endpoint that can be observed in real-time, are complex to organise, and the results are harder to analyse and interpret.

Sormani also discussed the potential for randomised registry trials, a type of RCT where the registry is used to select appropriate candidates for randomisation in the trial and collect standard outcomes collated in clinical practice. This design eliminates the lack of external and internal validity that can occur with RCTs and observational studies, respectively. Additionally, these trials can also be performed on a large scale and are low cost. Sormani explained that although this type of trial cannot be performed for new drugs, they could be used to consider drug repurposing, different drug dosing or combinations, and lifestyle interventions relevant to progressive MS.

In terms of improving the identification of individuals at high risk of progression, Marrie discussed a study by Salter et al.,[5] which highlighted how instrumental activities of daily living as an outcome measure was able to better discriminate progression amongst patients at a similar baseline disability level, and was better able to predict change in disability trajectories than the RAND-12. This could be taken forward into future trial design.

FOCUS FOR THE FUTURE

During the session, several of the expert speakers alluded to the fact that change is required to help identify novel therapeutics or targets for progressive

MS. Sormani stated: "It is clear that for clinical trials for progressive MS we need something new, some innovation." Given the lack of success in previous drug trials for progressive MS, Sormani discussed the "need to test drugs with a different mechanism of action" in a timelier fashion. Sormani further commented that "experiment beyond the fixed Phase II/Phase III design" is required alongside increased research into novel biomarkers targeting disease progression and joining multi-arm multi-stage initiatives. Sormani highlighted the MS Society-funded OCTOPUS trial, lead by Jeremy Chataway and Mahesh Parmar of University College London (UCL), UK, as an example of a multi-arm, multi-stage study in progressive MS. This trial will include a control group alongside three different treatment groups and an interim endpoint of brain atrophy, with a view to only continuing drugs that show a promising effect on brain atrophy to the clinical endpoint consisting of multiple outcome measures, including the EDSS, 9HPT, and T25-FW test.

Adil Harroud, Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Canada, highlighted how little is known about determinants of disease outcome and the potential role of genetics in progressive MS. They presented data showcasing the identification of a genome-wide genetic variant associated with MS severity, in which those homozygous for the risk allele had a shorter time to EDSS 6.0 by 4 years and a two-fold increase in brainstem and cortical pathology. Harroud concluded that the study could help to provide evidence to prioritise candidate drugs for progressive MS.

Sormani also explored the concept of using patient-specific outcome measures given the heterogeneity of progressive MS. This would involve pre-classifying patients according to disability status and an individualised pre-specified outcome, then running the trial to assess the progression of each specific outcome. However, this concept is in its infancy and requires further validation and regulatory approval.

The session concluded with a stimulating question and answer segment, and closed with Meilof thanking the speakers, audience, and the public.

References

1. McAdams M et al. Review of phase III clinical trials outcomes in patients with secondary progressive multiple sclerosis. Mult Scler Relat Disord. 2021;54:103086.
2. Marrie AR et al. Comparative responsiveness of the health utilities index and the RAND-12 for multiple sclerosis. Mult Scler. 2021;27(11):1781-9.
3. Chang I et al. Overall disability response score: an integrated endpoint to assess disability improvement and worsening over time in patients with multiple sclerosis. Mult Scler. 2022;28(14):2263-73.
4. Koch MW et al. Reliability of outcome measures in clinical trials in secondary progressive multiple sclerosis. Neurology. 2021;96(1):e111-20.
5. Salter A et al. New applications for independent activities of daily living in measuring disability in multiple sclerosis. Mult Scler. 2021;27(1):97-106.