Advancing Trial Design in Progressive Multiple Sclerosis

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Abstract

The failure of a majority of clinical trials in progressive MS has highlighted the need to reconsider how these trials are designed and conducted, and many areas deserve focus. Basic scientists are reconceptualising the pathophysiology of progressive MS into three broad areas: systemic inflammation, compartmentalized inflammation and non-inflammatory neurodegeneration, with the latter two becoming predominant as the disease progresses. This reconceptualization will guide the choice of experimental therapies. Previous clinical trials have highlighted how participant selection can have a significant impact on study outcome. Phase 2 biomarkers which are biologically stable, dynamically changing over time, and easy to assess in multi-centre studies are greatly needed. Shortcomings inherent in the Expanded Disability Status Scale is prompting the development and validation of better clinical measures. The standard 2-arm, fixed-duration trial paradigm has been challenged with new, innovative approaches that can test more therapies efficiently. International collaboratives such as the Progressive MS Alliance will support increased dialog with regulators, industry, and other funding agencies. Better engagement with people living with progressive MS will transform them from simply being the object of MS

therapies to partners in the search for therapies. Focused, targeted action will drive further development of effective therapies for progressive MS.

Multiple sclerosis (MS) typically starts as a relapsing remitting disease of the central nervous system, with repeated waves of inflammatory damage and neurologic dysfunction and is called relapse remitting MS (RRMS). After a decade or more, MS frequently transforms into a gradually progressive condition, with insidious worsening of neurologic function and is called secondary progressive MS (SPMS). In a minority of patients, the relapsing phase is skipped and the disease is gradually progressive from the very beginning and is called primary progressive MS (PPMS). Despite different antecedents, PPMS and SPMS appear to be more similar than they are different, so are often grouped together and called progressive MS.

Whilst the growing number of disease modifying therapies (DMT) in relapsing-remitting multiple sclerosis (RRMS) has been eagerly received,[1] the treatment landscape for progressive multiple sclerosis has remained stubbornly limited.[2] The few treatments for progressive MS is not from lack of effort. There have been dozens of clinical trials, and extensive effort has been expended to better understand the disease and potential treatment approaches. Despite these efforts, the treatment landscape is quite limited. This review examines different aspects of clinical trials for progressive MS. Further discussion of each of these topics is contained in the nine companion papers in this issue of Multiple Sclerosis Journal.

People Living with Progressive MS

Traditionally, people living with MS (PwMS) had little role in MS clinical trials except to volunteer their bodies as testing grounds for new therapies. More recently, however, PwMS have assumed greater roles in the search for treatments for their disease. Some of this shift comes from governmental fiat, such as where health authorities, grant organizations, and regulators require patient representation in the clinical trial process. The SPRINT-MS trial included a PwMS as a member of the Protocol Steering Committee, as required by the National Institutes of Health.[3] The DISCO study of MS therapy discontinuation has involved PwMS throughout the study's development and implementation, as required by its US federal funder, Patient-Centered Outcomes Research Institute. Foundations have integrated PwMS into their leadership structure, too, such as the Scientific Steering Committee of the Progressive MS Alliance (www.progressivemsalliance.org).

This shift has brought a recognition that PwMS are not simply the object of MS therapies, but can (and should) play important roles in the research process. They share personal expertise and knowledge about the disease, which can impact study protocols by incorporating participant needs and views. Their insights into the experience of living with MS can help focus the

development and choice of outcome metrics towards clinically meaningful measures. PwMS can be advocates for MS research by promoting financial support for research from funding agencies. PwMS can advocate throughout the MS community and elsewhere to raise awareness about the obstacles, limitations, and opportunities related to MS research. They can also improve study recruitment and retention, both through improvements in study designs that ease study participation and helping to educate the MS community regarding the importance of clinical trial enrolment and long-term participation.

This increased partnership comes with obligations. Clinical trials have traditionally had poor communication back to participants regarding trial results. This silence disenfranchises participants from the research process and dehumanizes their contributions. Those who organize clinical trials need to better plan how they share study results back to those who volunteered their bodies for the betterment of MS. PwMS also expect that their trial data is made available outside of the immediate trial investigators so that the data may better inform future research. Despite these expectations, clinical trial data sharing is still in its infancy.

In summary, the MS clinical trial enterprise is learning to better partner with PwMS to improve and accelerate the clinical trial process. This partnership will benefit both PwMS and the research enterprise.

Lessons Learnt from Progressive MS Trials

The disappointment that derived from several decades of progressive MS trials with negative outcomes has been buoyed lately by several positive progressive MS clinical trials. Simvastatin,[4] biotin,[5] ocrelizumab,[6] and siponimod[7] have all demonstrated positive outcomes in phase 2 or 3 trials, and these results have pointed towards potential treatment avenues. This excitement is tempered by the anti-inflammatory effects of some of these therapies and sub-group analyses that suggest that the predominant benefit is derived from the subset of participants with active inflammation before the trial.

The positive and negative trials provide insight into important aspects of the trial population. Revised phenotype criteria published in 2014 now allow for relapsing and progressive MS to occur simultaneously, thus recognizing the overlapping aspects of the inflammation that underlies relapsing MS and the other, yet-to-be-defined pathophysiology of progressive MS. Age, disease severity, co-morbidities and rapidity of progression are all now recognized to

be important potential factors impacting study outcome and response to treatment. Enrolling subjects who are likely to have progression over the course of the trial is important, since those who don't progress will not contribute to measuring a therapy designed to slow progression. Several efforts are underway to better identify these subjects.

Pathology

The disappointing outcome of so many therapies in progressive MS trials has prompted basic scientists to reconsider the previously held notions regarding the pathophysiology of progressive MS.[8] A cardinal presumption has been that relapsing and progressive MS have the same underlying pathophysiology, but that appears unlikely. Instead, there are a myriad of potential pathologies, including B and T lymphocyte dysregulation, primary demyelination and neurodegeneration. This state of affairs is dynamic, and likely shifts over the course of the disease, which is highly relevant for timing of target intervention. Potential links in the chain of injury in progressive MS include microglial activation, reactive oxygen/nitric oxide, cellular injury, mitochondrial damage, ionic imbalance, compounded by vascular hypoperfusion and iron accumulation. The end-pathology can be tri-categorised: systemic inflammation, compartmentalized inflammation and

non-inflammatory neurodegeneration. As MS evolves into progressive MS, the role of systemic inflammation appears to wane and either compartmentalized inflammation or neurodegeneration (or both) become predominant. Novel approaches are required, particularly for compartmentalized inflammation and neurodegeneration.

The failure of oligodendrocyte precursors to differentiate and remyelinate naked axons in MS remains a mystery and provides an adjunctive treatment approach for progressive MS. The reasons for the failure of remyelination is not known but may involve loss of endogenous progenitor cells, the blockade of differentiation into myelinating cells, and a generally hostile tissue environment. The disappointing effect of a monoclonal antibody specifically developed to target remyelination highlights the challenge for remyelinating therapies.[9]

Participant Selection

When designing a clinical trial a fundamental parameter is the type of patient that is entered into the process, which is of course a human experiment. If inclusion criteria are too wide, it may lead to an amplification of natural variability, which may drown out any nascent signal of therapeutic

benefit. On the other hand, if entry criteria are too stringent, then external validity and generalizability become compromised.

The PROMISE trial of glatiramer acetate in PPMS found increased rates of progression for males and those with either CSF oligoclonal bands or gadolinium enhancement (GdE) at baseline.[10] The OLYMPUS trial of rituximab in PPMS found that younger patients and those with GdE at baseline were more likely to benefit from therapy.[11] These findings directly guided the inclusion criteria for the ORATORIO study of ocrelizumab, where subject age was capped at 55 years and disease duration at 10-15 (depending upon disability level). Similar to OLYMPUS, the ORATORIO study found a greater clinical benefit in the 25% of subject with GdE at baseline.[6] By limited age and disease duration, the generalizability of the ORATORIO study to the broader PPMS patient population, with older age and longer disease duration, is unknown.

Detailed analysis study of the population characteristics from progressive MS trials is instructive in guiding eligibility requirements for the next tranche of trials. Sub-group analyses provides insight into both subject characteristics that predict future disability as well as characteristics that are more likely to respond to therapeutic intervention.

Clinical Measures

Measuring progression in clinical trials has been challenging, and the optimal outcome measure is not well established.[12] The traditional Expanded Disability Status Scale (EDSS) is limited in its scoring vagaries and sensitivity to change over time. Electronic scoring of the Neurostatus EDSS has become available which has reduced rater scoring error. Alternative clinical measures have arisen from the MS Functional Composite, including time 25-foot walk, 9-hole peg test, low contrast letter acuity, paced auditory serial addition test (PASAT), and the symbol digit modality test (SDMT). These newer measures have demonstrated subject validity, appropriate scale behaviour and relevance of change over time, although each measures only a small portion of neurologic function affected by MS. Cut-points for meaningful changes in these metrics have been developed and will continue to be validated and refined by subsequent studies.

Composite outcomes combine metrics together to define progression and have been used with good success in trials such as the INFORMS trial of fingolimod,[13] where over 70% of subjects demonstrated sustained progression on the composite over 3 years. The optimal mixture of measures and operative logic (i.e. combining measures using “or” vs “and”) is not yet established.

Increased sensitivity using composites need to be further validated, including how the measures are weighted.

Cognition is highlighted as a particular area of interest. The replacement of PASAT by SDMT in clinical trials appears secure, although SDMT is an incomplete cognitive test. The optimal composition of cognitive testing batteries is unknown and needs to balance completion time (and thus subject and investigator burden) with sensitivity. Cognition is a very common symptom reported by PwMS and therefore deserves a prominent place in future clinical trials.

Patient Reported Outcomes (PROs) remain an important component of clinical trials, since they provide grounding to patient's experience of the disease. There continues a tension between MS-specific (e.g., MSIS-29) and MS-non-specific (e.g., EQ5D) measurements. In relapsing MS trials, PROs have often not demonstrated benefit of therapy, despite positive outcomes on relapses and sustained progression of disability. As a result, PROs remain an adjunctive outcome, and whether they can become primary outcomes in disease-modifying treatments in progressive MS remains an unanswered question.

In summary, EDSS has yet to be toppled from a regulatory and scientific standpoint. However, increasingly concerted approaches using a variety of

substantial datasets continue to evolve the clinical measurement of progressive MS. Their outcome promises a richer and more dynamic clinical measurement stick in the future.

Phase 2 Trial Biomarkers

The development of therapies for progressive MS can be accelerated by effective Phase 2 trial outcomes. Phase 2 trials are intended to provide proof-of-concept evidence of efficacy through short trials, involving a small number of subjects, using a biomarker as the primary outcome. In relapsing MS, phase 2 trials are typically six months in duration and involve 50-75 subjects per treatment arm. A similar structure is desired for progressive MS. Where new T2 or gadolinium enhancing lesions are the most common biomarker outcome for phase 2 trials in relapsing MS, the equivalent biomarker in progressive MS is unknown. Fluid, electrophysiology, and imaging biomarkers provide attractive candidate biomarkers.

Fluid Biomarkers. Neurofilament light (NfL) is a major protein contained in axons and is frequently shed into the cerebrospinal fluid when nervous tissue is damaged. Any damage can lead to increased NfL in CSF, which in MS includes neuroinflammation and neurodegeneration. NfL crosses readily into the blood stream, and recent studies have demonstrated blood NfL to be a

good estimate of NfL in the CSF.[14] NfL has been shown to be a good measure of treatment response in RRMS and also correlates with disability progressive in progressive MS. Ongoing studies will define normative values, biologic variability, and optimal testing methods. Several ongoing clinical trials will evaluate the potential use of NfL as a biomarker in progressive MS trials.

Additional potential fluid biomarkers include matrix metalloproteinase-9, chemokine ligand 13, chitinase-3-like-1, and osteopontin. The biologic variability, testing stability, standardization for testing, and clinical relevance is less known for these biomarkers, which make them further from potential employment in a progressive MS trial.

Electrophysiology Biomarkers. Evoked potentials are quantitative measures of neurologic function and could be useful as biomarkers in progressive MS trials. Multi-focal visual evoked potentials were used as the primary outcome in the RENEW study of a remyelinating therapy of acute optic neuritis,[9] although has not yet been used in progressive MS. Like other biomarkers, the biologic variability, reproducibility, dynamic change over time, and multi-centre standardization is still being developed.

Imaging Biomarkers. Whole brain atrophy has been the most accepted and utilized imaging outcome for phase 2 trials of progressive MS.[15] Limitations include biologic variability, its slow change over time, and it being only a single

value per subject, which limits granularity of assessment. Regional atrophy (i.e. grey matter volume and thalamic volume) have received some attention, since they appear to be more responsive to RRMS treatments. Optimal measurement techniques remain unknown. Spinal cord atrophy may provide a more specific measure of injury relevant in progressive MS. Challenges with spinal cord atrophy include its very small size, motion from CSF flow, and its presence on only the most caudal brain image slices, where artefacts are more likely. Although some have advocated for registration-based methods over segmentation-based for atrophy measures, the evidence supporting one atrophy method over another is too limited at present.

Advanced imaging methods such as magnetization transfer ratio, diffusion tensor imaging, and optical coherence tomography have the potential to provide more pathologically specific measures of tissue integrity with greater dynamic range and change over time. The voxel-level characterization available with advanced MRI measures may provide a tissue-level granularity that makes them more powerful metrics than either whole-brain or regional atrophy measures. Challenges with advanced imaging methods include a limited understanding of their biologic variability and dynamic change over time, the challenges in multi-centre implementation, and little experience using them in multi-centre trials.

A challenge for all advanced imaging measures is the potential impact of changes in technology over time. MRI scanners frequently receive upgrades, and the impact of changes in pulse sequence, coils, and other hardware is mostly unknown and difficult to predict. Currently, clinical trial analyses exclude intervals across a scanner change, which significantly reduces the statistical power of trials. Several ongoing trials using these measures will provide important insight into their potential use as biomarkers in progressive MS, as well as methods to overcome some of the technical challenges.

Clinical Trial Design

A significant threat to finding effective therapies in progressive MS is flawed trial designs. Several important aspects of trial design have become recognized recently.

The population enrolled in the trial is important. The presence of inflammatory activity at baseline is important with anti-inflammatory therapies, since subjects without inflammatory activity are less likely to respond to anti-inflammatory therapies. Age, sex, duration of disease, disability levels, and rate of progression can each have an impact on the resultant disease course and response to therapy.

The choice of phase 2 outcome is key to any trial's design, and the lack of consensus regarding a reliable, sensitive, dynamic biomarker for progressive MS is a challenge. Brain atrophy is the current standard, but therapeutic lag and pseudo-atrophy from anti-inflammatory effects of some therapies can confound measures of brain atrophy. Delaying baseline can help reduce this confounding, but decreases study power by shortening the interval of outcome measurement.

Clinical outcomes in phase 3 trials also pose a challenge for trial designs. EDSS has poor reliability and statistical characteristics, and composites have met with resistance from regulatory agencies. Quality of Life metrics have a similarly difficult statistical performance which make them very difficult to power using feasible sample sizes.

Finally, the traditional placebo vs active trials using frequentist statistical modelling has been challenged lately. Adaptive trials, where treatment choices are dynamically influenced by the contemporary study experience, allow for more therapies to be evaluated simultaneously, with the better therapies emerging over the course of the study. Adaptive trials can be based upon Bayesian statistical methods, which can provide flexibility in the design and analysis of study results.

Regulatory and Funding Aspects

Progressive MS trials are not conducted in isolation, but rather within a regulatory environment and using significant financial support. Phase 3 outcomes require regulatory acceptance for market approval. In 2015, the European Medicines Agency issued guidelines that encouraged the development of alternative scales to assess disability, but acknowledged that at that time, EDSS was the only validated outcome measurement to determine disability.[16] A common misperception that biomarkers need regulatory approval to be used in progressive MS phase 2 trials. Most progressive MS phase 3 trials had no phase 2 trials demonstrating efficacy, which highlights how regulators don't require any evidence of efficacy from phase 2 trials. Similarly, T2 and gadolinium-enhancing lesions are typical primary outcomes for most RRMS phase 2 trials, yet they have never received formal regulatory approval for this purpose. The regulatory focus in phase 2 trials is on safety; proof-of-concept efficacy (i.e. using a biomarker) generally is not a regulatory concern in phase 2 trials.

Phase 2 and 3 clinical trials in progressive MS costs between tens and hundreds of millions of US dollars to conduct. Commercial support for progressive MS trials has been fuelled by the commercial success of approved

relapsing MS therapies and the promise of similar success in progressive MS. This euphoria has waned after so many studies failed to meet their primary outcomes. A return to basics is needed to reinvigorate the process. This includes a better understanding of the true pathophysiology of progressive MS; benchtop models of progressive MS to test potential treatment targets and ligands; useful phase 2 biomarkers; sensitive clinical measures of disability progression and its improvement from therapies intended to restore function. Increased support for progressive MS trials will results from improvements in the process of developing and testing the therapies.

The vital need to gather together academic, commercial, and patient advocacy organizations is realized with the Progressive MS Alliance and its Industry Forum. The Alliance has already provided a useful forum for dialog with federal regulators. To promote a continuous and meaningful dialogue is at the heart of the endeavour, and key priority areas of research have been identified.

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