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Evolution of clinical trials in multiple sclerosis

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Abstract: Clinical trials have advanced the treatment of multiple sclerosis (MS) by demonstrating the safety and efficacy of disease-modifying therapies (DMTs). This review discusses major changes to MS clinical trials in the era of DMTs. As treatment options for MS continue to increase, patients in modern MS trials present earlier and with milder disease compared with historic MS populations. While placebo-controlled trials for some questions may still be relevant, DMT trials in relapsing–remitting MS (RRMS) are no longer ethical. The replacement of the placebo arm by an active comparator arm in trials have raised the cost of trials by requiring larger sample sizes to detect on-study changes in treatment effects. Efforts to improve trial efficiency in RRMS have focused on exploring adaptive designs and relying on sensitive magnetic resonance imaging measures of disease activity. In trials for progressive forms of MS (PMS), the lack of sensitive outcome measures that can be used in shorter-term trials have delayed the development of effective treatments. Recent shifting of the focus to advancing trials in PMS has identified paraclinical outcome measurements with improved potential, and the testing of agents for neuroprotection and remyelination is in progress.

Keywords: multiple sclerosis, clinical trials, trial design, diagnostic criteria, outcome measure, progressive multiple sclerosis

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Introduction

The advancement of new therapeutic agents for multiple sclerosis (MS) relies on well-designed clinical trials to establish their safety and efficacy. Over the last two decades, clinical trials in MS have established a success rate of 27%, defined as passing phase I, II, III and United States Food and Drug Administration (US FDA) approval, almost tripling the overall industry rate of 10%.[1] As a result of now having 15 approved disease-modifying therapies (DMTs) for relapsing–remitting MS (RRMS), there is a greater challenge to improve the existing options and to achieve prolonged remission. The increased availability of treatment along with revisions in the diagnostic criteria have changed the clinical trial population and restricted the implementation of placebo-controlled trials. At the same time, an increased understanding of the pathophysiology and natural history of the disease have spurred the development of new outcome measurements and refinement of existing metrics. Despite numerous successes in advancing therapies for RRMS, similar progress has not been achieved for patients with progressive forms of MS (PMS), and previously failed trials in PMS have delineated the challenges that must be overcome to develop treatments for PMS. The design of MS trials must take its dynamic landscape into consideration and account for the differences between modern and historical trials. This article will review the changing characteristics of MS trial patients, the shift from placebo-controlled trials to active comparator studies, and traditional and new outcome measurements. In addition, the challenges and progress in PMS trials will be discussed.

Changes in trial populations

The characteristics of RRMS trial populations have changed over time, largely in response to shifting methodologies in patient diagnosis and selection as well as the availability of multiple treatments. Patients in recent trials are presenting with lower disease activity and slower clinical progression.[2] This is evident in the annualized relapse

rates (ARRs) in the treatment groups from historical trials between 1993–2002 that have ranged between 0.5 and 0.87 whereas subsequent modern-day trials have reported ARRs between 0.16 and 0.37.[3] While some of the reductions in relapse rates are likely due to the more rigid definitions in trials used to confirm relapses, there nevertheless appears a steady decline in the ARR over time. A report analyzing the ARR in RRMS trials over time demonstrated a reduction of 0.37 relapses in the treatment arms and 0.36 in the placebo arms over a 10-year study period.[4] In addition, patients who were relapse-free in the placebo groups of RRMS trials experience a longer time to their first relapse.[2] The trend of MS trial patients presenting with milder disease over time is a result of multiple processes. In this section, we explore the changes in the MS trial population and its implications.

Changes in diagnostic criteria

The MS diagnostic criteria and its subsequent revisions have made it easier to diagnose the disease and this has resulted in many patients receiving an earlier diagnosis.[5,6] Since the 2010 revision of the McDonald criteria, a diagnosis of MS can be made in a single time frame, in which lesions on a single magnetic resonance imaging (MRI) scan can fulfill both criteria for dissemination in time (DIT) and dissemination in space (DIS). This contrasts with previous criteria in which the diagnosis required subsequent clinical presentations or MRI to fulfill DIT. The latest revision of the McDonald criteria in 2017 further broadened the diagnostic parameters and included the presence of oligoclonal bands in the cerebrospinal fluid to substitute for DIT when the initial MRI findings did not fulfill this requirement.[7] In addition, cortical lesions, and symptomatic lesions excluding the optic nerve, may now be counted as MRI evidence of DIS or DIT. By broadening the diagnostic criteria, more patients are likely to be diagnosed earlier whereas they previously would not be diagnosed by an earlier version of the criteria.

A consequence of earlier diagnosis resulting from changes in diagnostic criteria is that the overall clinical course of MS appears to improve. The average MS patient today has milder disease compared with those diagnosed using the older criteria. However, this may have resulted in lead-time bias, in which earlier diagnosis appears to improve the disease course as patients take longer to accumulate neurological disability. This would lower the ARR by providing an observed time with fewer relapses relative to the older definitions, such as the Poser criteria. This lead-time bias would also lead to the appearance of less virulent disease, at least in the short term. Whether this is occurring is difficult to separate from potential confounders such as improved availability and efficacy of therapies.

Likewise, a portion of patients with clinically isolated syndrome (CIS) who are at high risk of developing MS will have a diagnosis of MS under the new criteria. The reassignment of patients who are at a higher risk within the CIS group to those having milder disease in the MS group results in the improved overall prognosis of both groups, an effect known as the Will Rogers phenomenon.[8] This has been demonstrated since the first iteration of the McDonald criteria by a retrospective analysis showing that 50% of patients with CIS would progress into definite MS within a year by the 2001 McDonald criteria compared with only 20% under the previously used Poser criteria.[9] Currently, there is no evidence as to whether the 2017 revision will select patients with less active disease. Recently, a retrospective analysis on reaching the diagnosis of MS under the latest revision of the McDonald criteria compared with the 2010 revision, concluded that the 2017 revision expedites diagnosis without compromising diagnostic accuracy.[10]

Availability of treatment

The increasing availability of treatment for RRMS has also affected patient enrollment in trials. With multiple DMTs available, there are motivations for high-risk patients not to enroll in a clinical trial as these patients may opt to select a proven therapy rather than enroll in a trial and risk receiving a placebo or a medication with unknown safety or efficacy profiles. Likewise, patients currently involved in trials who experience a relapse may be rescued and removed from the trial to start a proven therapy, thus leaving those whose disease activity is relatively well-controlled during the trial period to complete the study. There are suggestions that over time, withdrawals from therapy have been increasing and even mandated on the occurrence of relapses or progression, thus reducing the opportunity to have subsequent outcome events reducing the ARR and other event rates over the course of the study.

On the other spectrum, patients who are treatment nonresponders may be interested in seeking new options by enrolling in a trial. However, some trials exclude enrollment of patients with extensive exposure to prior DMTs.[11,12]

Additional considerations

Other factors have been proposed to account for the changing MS trial population. For example, increasing physician and patient awareness of the disease and accessibility to MRI scanning has led to earlier diagnosis and initiation of treatment.[13,14] Improved standards of care for MS and accessibility to DMTs have resulted in better overall management and thus, lower disease activity in the overall MS population. Modern-day trials allow patients to enroll closer to their time of diagnosis by reducing the requirement of the number of relapses prior to screening. Whereas most early trials required at least two relapses over the course of 2 years, many contemporary trials allow for enrollment with just one relapse over the past year. In addition, recent trials use more stringent and objective definitions of relapse requiring evaluation by a neurologist and measurable increases in the Expanded Disability Status Scale (EDSS) functional system subscores.[15] Together, these changes further substantiate the shift of the MS trial population towards milder disease activity.

Implications

The changing MS trial population complicates the comparison of results from different studies, especially those from different times.[16] Assessing whether one DMT is superior to another is challenging without a head-to-head comparison of the two agents in a randomized controlled trial, yet it is impractical to conduct head-to-head studies of all available agents. As trial patients present with milder disease, it becomes more difficult to generate on-study changes with traditional designs, and therefore larger group sizes and longer study duration are required. At the same time, it is no longer practical to design studies based on assumptions drawn from historic trials. Studies that are designed and statistically powered according to findings from earlier trials may overestimate disease activity and underestimate the number of patients enrolled to be able to detect treatment differences. There is a need for more efficient designs and sensitive outcome measurements.

Trial designs

The rapid expansion of treatment options for RRMS has led to changes in clinical trial designs over time. The era of placebo-controlled trials to establish new DMTs has ended due to the ethical concerns when existing therapies are available, and new agents are now assessed through comparative studies using established DMTs. The increased costs of large trials and high demand for participants have spurred the need for more efficient designs, while increased therapeutic options calls for pragmatic studies to determine the real-world applicability. The strength and limitations of MS trial designs are summarized in Table 1.

The ethics of placebo in RRMS trials

New treatment options for RRMS have led to the decline of placebo-controlled trials due to the ethics and marketing concerns of performing such studies when multiple effective therapies exist. The 1990s saw the approval of the first MS therapies, including interferon β preparations and glatiramer acetate.[17–19] These trials relied on the use of a placebo group to demonstrate the efficacy of the investigated agent. Subsequent pivotal phase III trials of new therapies incorporated a placebo group until the approval of alemtuzumab, which in 2014 became the first US-approved agent without comparison with a placebo.[20,21] However, the ethics of using a placebo in MS trials have been in discussion since much earlier.

Following the availability of the first injectable DMTs, the National MS Society organized an international task force in 2000 to discuss and publish proceedings on the ethical use of placebos in MS trials, and its recommendations were further revised in 2008.[22,23] The group concluded that participation in placebo trials is still ethical for patients who decline or fail available agents or when established therapy is not available at the time, such as in PMS. In countries without access to any DMTs, placebos may also remain ethical, but active comparator trials still seem more appropriate. Some countries, such as Brazil, will not allow placebo-controlled trials if the trial is not conducted in the country originating the trial. In all cases, appropriate informed consent and information on available therapies must be provided.

Controversies exist on whether placebo trials are justified, and despite recommendations restricting the use of placebo in RRMS trials, subsequent

Table 1. Advantages and disadvantages of MS trial designs.

Trial design	Advantages	Disadvantages
Placebo-controlled	Most rigorous test of treatment efficacy; requires fewer participants than active comparator trials	No longer ethical in RRMS trials due to availability of proven therapies
Active comparator	Alternative to placebo-controlled trials and still capable of detecting treatment effect	Requires increased sample size to detect significant treatment differences
Combination	Potential to increase efficacy by combining therapies	Increased costs and side effects from added treatment; potentially antagonistic interactions; increased design complexity
Adaptive	Flexible and efficient designs to reduce sample size, exposure to harmful or ineffective treatment, and trial duration	Requires detailed planning and review of interim data as well as sensitive short-term outcome measures
Pragmatic	Real life evaluation of treatment effectiveness; high external validity; results are more likely to inform practice	Greater design challenges due to heterogeneity of treatment effect; larger sample size and duration needed to determine effectiveness

MS, multiple sclerosis; RRMS, relapsing–remitting MS.

phase III trials of fingolimod, teriflunomide, and dimethyl fumarate had approximately 1500 patients exposed to placebo treatment.[24] Many researchers and organizations have taken a middle ground with regard to using a placebo when proven therapies are available.[25] The continued use of a placebo is backed by claims of the changing natural history of MS and indication that data from previous placebo groups are no longer valid.[26] However, as growing evidence surmounts to the detrimental effects of delaying initiation of DMT for RRMS, the use of a placebo in RRMS trials have ended.[27]

Active comparator designs

The past decade saw a gradual replacement of placebo designs by active comparator trials. The pivotal phase III trial of peginterferon β-1a marked the last placebo-controlled trial of a therapeutic agent for RRMS.[28] Subsequent published phase III trials of daclizumab and ocrelizumab, as well as the recently concluded phase III trial for ozanimod, have been conducted with active comparator arms.[29,30] These trials have shown that active comparator studies are feasible to detect both the efficacy and superiority of new agents. On the other hand, the use of an active comparator arm instead of a placebo reduces on-study changes between both groups, resulting in more patients needed to observe a significant and meaningful treatment effect. Modern-day trials have reflected this change. Whereas early trials typically enrolled around 200 patients, modern trials have frequently enrolled more than 1000 patients. The increasing costs of conducting large-scale trials have put a strain on existing resources, and there is a need for more efficient designs.

Combination trials

Combination trials seek to answer the question of whether multiple therapies administered together have greater efficacy than either alone. Studies are designed on the premise of using different agents with complementary or synergistic mechanisms of action.[31] In this regard, the most rigorous study to date examined the effects of glatiramer acetate and interferon β-1a administered together, which did not show a benefit in using both drugs over the more effective agent, glatiramer acetate.[32,33] Other studies combining DMTs with hormonal therapy[34] or statins[35] have shown mixed results. Significant drawbacks of employing combination trials include the potential antagonistic mechanisms of action among study agents, compounded costs and side effects, and increased size and complexity of the trial design.[36] While these reasons have deterred

combination trials in MS, there may be a role in the future as we progress in understanding the disease pathophysiology and developing more therapeutic options.[37]

Adaptive designs

Adaptive designs offer flexible and efficient trial methods that allow for preplanned modification of the study protocol after an interim analysis. This allows for flexibility in cost and trial duration. While adaptive designs have seen use in other fields of medicine, current experience with adaptive designs in MS is just emerging. The phase II trial of siponimod for PMS was the first and only published MS trial to date that employed an adaptive design to evaluate the safety and tolerability of the study agent and to determine its dose-efficacy response curve.[38] The study randomized one cohort of patients to receive 10 mg, 2 mg, or 0.5 mg of the study agent or placebo and evaluated the outcome of combined unique active MRI lesions at month 3. An interim analysis was performed, and based on an estimation of which doses would be needed for the optimum dose–response characterization, a second cohort of patients were randomized to receive 1.25 mg and 0.25 mg of the study drug. Evidence for the further efficacy of siponimod was recently published in a double-blind randomized placebo phase III trial.[39] The design of adaptive trials demands meticulous planning and a detailed interpretation of the interim results and navigation of a complex review process. It also requires a sensitive short-term outcome measure on which to base interim decisions and long-term outcomes to assess treatment efficacy. Adaptive designs for MS are nascent and their prevalence remains to be seen.

Pragmatic trials

As therapeutic options for MS broaden, there is a growing need for evidence demonstrating applicability of clinical trial results to routine clinical practice. In contrast with explanatory trials, which measure efficacy under controlled settings, pragmatic trials are designed to evaluate treatment effectiveness in the real-world setting, producing results that are more generalizable and applicable to clinical practice.[40] Despite the distinction between explanatory and pragmatic trials, actual trials fall on a spectrum between the two categories as characterized the Pragmatic–Explanatory Continuum Index Summary (PRECIS) tool and its subsequent revision (PRECIS-2).[41,42] The tool helps trialists to ensure their design decisions match the trial's intended purpose.

Just as explanatory trials face the challenge of requiring a large sample size with enough follow-up time to detect significant treatment effects, the issue is even greater in pragmatic trials when selection criteria and interventions are less controlled. A purely pragmatic trial in MS is almost unattainable and will almost certainly include components towards the explanatory end of the spectrum. As adeptly summarized by Ford and Norrie in a publication of pragmatic trials in the *New England Journal of Medicine*, 'a pragmatic approach to pragmatism would be to adopt the features of pragmatic trials whenever feasible and sensible and when such features do not compromise trial quality and the ability to answer the clinical question of interest.'[43]

Traditional and new outcome measures

Relevant and sensitive outcome measures are key to the assessment of a new drug's efficacy. Traditionally, phase II trials assess the short-term effects on MRI outcomes, while phase III designs focus on more overt clinical outcomes. While this model has standardized the development of the currently available DMTs, the outcome measures used are imperfect, largely due to the heterogeneity of the disease. The paradigm of the MRI in phase II may be limited to the mechanism of action of the DMTs; most, if not all, have addressed inflammation as the target. New drugs may require different measures either on MRI or other biomarkers. Variations in disease presentation across the population and even within an individual over time have led to challenges in the development of methods to assess treatment efficacy. This is further complicated by the need to capture changes within a short clinical trial duration for a disease with a prolonged clinical course. Traditional clinical and imaging outcome measures continue to show utility in modern trials while new measures in advanced imaging outcomes, biomarkers and composite outcomes have diversified options for choosing study endpoints. The advantages and disadvantages of outcomes measures in MS trials are summarized in Table 2.

Clinical outcome measures

Clinical outcomes play an important role as the primary endpoint of pivotal phase III trials.

Table 2. Advantages and disadvantages of outcomes measurements in MS trials.

Outcome measure	Advantages	Disadvantages
EDSS	Established and universally accepted clinical outcome measurement; familiar to clinicians and regulators	Inter-rater variability; heavy emphasis on walking; exclusion of cognitive impairment; nonlinear scale
MSFC	High reliability, validity, and sensitivity; versatile in evaluating various levels of disability	*z*-scores are abstract and difficult to interpret
Patient-reported outcomes	Patient-centered assessment of disease or treatment impact	Inherently subjective; limited use in disease-modifying therapy efficacy trials
MRI lesions	Objective and quantifiable; High sensitivity in detecting subclinical disease activity; particularly useful as primary outcome measures in phase II trials	Lesions do not reflect degree of clinical disability
Brain atrophy	Correlations with disability and cognitive impairment; measurement of neurodegeneration	Requires longer time to detect atrophy changes; multiple variables may confound measurements
OCT	Fast, inexpensive, noninvasive technique; association with neurodegeneration	Limited evaluation of central nervous system function and disease burden
Fluid biomarkers	Provides insight into disease pathophysiology; detects ongoing disease process; easy to obtain from serum	No established biomarkers; current biomarkers lack specificity
Combined outcomes (NEDA-3 and NEDA-4)	Better predictive value for disability progression than individual measures can identify treatment response	Cannot measure specific outcomes; no standardized set of components

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; NEDA-3, no evidence of disease activity including absence of new lesions, confirmed EDSS worsening and relapses; NEDA-4, as NEDA-3 in addition to absence of significant brain volume changes; OCT, optical coherence tomography.

Assessments of relapse and changes in the EDSS score have been the oldest and most widely used clinical outcome measures. They each capture distinct pathophysiologic processes of the disease. Whereas relapse rates measure inflammatory activity, changes in the EDSS reflect accumulation of clinical disability from inflammatory or neurodegenerative disease processes. The EDSS is universally familiar to MS clinicians and accepted by regulators,[44,45] but it is marked by shortcomings in its variability between examiners, heavy emphasis on walking, limited impact of cognitive impairment and nonlinearity. The imperfections of the EDSS have led to the development of the MS functional composite (MSFC),[46] which covers three major MS domains, can be assessed quickly and reliably, and gives a *z*-score on a continuous scale. However, *z*-scores are abstract and difficult to interpret clinically, which has limited the widespread use of the MSFC. Despite its imperfections, the EDSS currently remains the most accepted clinical outcome measure and will likely remain so for the near future. Recently, electronic scoring of the EDSS has been developed and has shown an increased consistency of EDSS scoring,[47] and it has seen use in the phase III trials of ocrelizumab[30] and siponimod.[39]

Over the past decade, patient-reported outcome (PRO) measures have increasingly been used as

complements to objective clinical measures and provide important information on subjective outcomes, such as evaluations of subjective symptoms, satisfaction with treatment, and quality of life.[48–50] They offer an additional facet in the assessment of treatment risks and benefits. Nevertheless, the subjectivity of PROs typically limits their use to a secondary outcome measure for DMT investigations.[51] Their use as primary outcomes for symptomatic therapies may be appropriate.

Neuroimaging outcome measures

Neuroimaging outcome measures provide additional information to supplement clinical measurements of treatment efficacy. Most commonly used are MRI measurements of lesion load or atrophy, which provide objective and highly sensitive measurements of current and past disease activity. Inflammatory activity can be quantified as focal lesions on T2 MRI sequences or T1 gadolinium-enhancing lesions and have shown a correlation with relapse rate.[52,53] This important metric has allowed for rapid development of DMTs for RRMS due to its use as the primary outcome in short-term phase II trials. The ability to detect reductions in lesions on MRI associated with treatment allows for quick progress into phase III trials.[54] The accrual of disability as reflected by neurodegeneration is measured by brain atrophy. This has been commonly assessed either as total brain parenchymal volume or fractional volume, defined as the ratio of brain parenchymal volume to total volume within the brain surface contour.

MRI outcome measurements have undergone refinement as the understanding of the disease process continues to develop. Composite imaging outcomes of combined unique active lesions have seen use in a growing number of trials to assess total new or enlarging T2 or gadolinium-enhancing lesions. Regional atrophy is increasingly explored as a more sensitive measurement of changes reflective of associated deficits, and areas of the thalamus and cerebellum may be more sensitive to changes.[55,56] Gray matter atrophy has been shown to have more clinical correlation than white matter atrophy and is more sensitive to changes.[57]

Optical coherence tomography (OCT) is a noninvasive method to image the retina and characterize pathology of the optic nerve.[58] By visualizing the unmyelinated axons of the retinal nerve fiber layer (RNFL), OCT can directly assess axonal injury. In MS patients, the RNFL is thinner than in healthy people, regardless of a previous history of optic neuritis, supporting its role as a unique *in vivo* model of neurodegeneration.[59–62] OCT has been used as an outcome measure in a few clinical trials in PMS without evidence of neuroprotective effects.[63–66] Despite its current lack of prevalence in clinical trials, OCT as a fast, inexpensive, and noninvasive approach to evaluate neurodegeneration, continues to prompt further investigation into refining the method.

Advancements in imaging techniques have led to the development of new outcome measures. Magnetization transfer ratio (MTR) is an MRI technique used to assess tissue integrity by correlating it with axonal loss in MS lesions. Whole brain MTR has been used in several trials,[28,63,64,67,68] while regional MTR has been used in the phase III trial of laquinimod for RRMS.[69] While imaging outcome measurements are not likely to replace clinical endpoints in trials, they provide important information that supplements data on the efficacy of novel agents.

Fluid biomarkers

Clinical and radiologic outcome measures have served as the cornerstone of assessing the therapeutic efficacy of drugs and disease activity; however, they provide limited assessment of the pathophysiological disease process, such as inflammation, axonal injury, and demyelination. Early search for biomarkers in the spinal fluid of MS patients hoped to identify outcomes that could be used in trials, but these efforts have not yielded promising results. In recent years, several biomarkers for MS have shown potential for diagnosis, prognosis, monitoring disease activity and treatment response.[70] Although currently there are no established biomarkers in use in clinical trials, among the most promising is neurofilament light chain (NFL).[71] NFL is a subunit of neurofilaments that compose the axonal and dendritic cytoskeleton. It is released during axonal injury, making it a marker of axonal damage.[72] In addition to its presence in the cerebrospinal fluid, NFL can also be detected in the serum due to using the ultrasensitive single molecule array (Simoa) technology.[73,74] Serum NFL has been shown to correlate with relapses, EDSS scores, MRI lesions, and brain and spinal cord atrophy,[75–78] and its levels have shown

a decrease in patients treated with DMTs.[79–82] Its downside is the lack of specificity, and levels may be influenced by many comorbidities or conditions. With an increased availability and understanding of NFL and disease activity, NFL may become the first fluid biomarker to be used to monitor therapeutic effects in future randomized clinical trials and we may eventually see its use in the clinical setting.

Combined outcome measures

Other new outcome measures have integrated domains to achieve a more holistic evaluation.[83] The concept of disease activity-free status in MS was first explored in the natalizumab phase III trial,[84] and it was later defined as 'no evidence of disease activity' (NEDA) to reflect the absence of relapses and no progression of disability or new MRI activity. NEDA has been used in some phase II[85,86] and phase III trials.[20,21,32] The combination of outcome measures increased the predictive value of disability progression compared with individual clinical or MRI metrics.[87] The drawback of using NEDA lies in the inability to assess its effects on specific outcomes, since clinical and radiological activity are all combined into one assessment that is heavily dependent on timing. Currently, NEDA is still undergoing refinement as it remains unclear which optimal components to include and how frequently they should be assessed. In addition, brain volume as a marker of neurodegeneration has been proposed to be included in a revised measure referred to as NEDA-4.[88] As the concept of NEDA continues to evolve, it becomes important to establish standardized definitions to facilitate universal interpretation and demonstrate its validity and reliability across studies.

Clinical trials for progressive MS

While substantial progress has been made in the advancement of therapeutic options for RRMS, progress for PMS remains limited and treatments are much needed, and only recently has a DMT been approved for PMS.[89] The challenges in advancing therapeutics in PMS arise from a limited understanding of the pathogenesis of PMS and difficulty defining and assessing the disease course, as well as apparent confounding with the aging process. This contrasts with the established trial methodology for RRMS in which changes in focal MRI lesions in phase II trials allow for the accurate prediction of clinical reductions in relapse rate in phase III trials. Trials for PMS do not have established enrollment criteria owing to the lack of a uniform clinical definition of the disease.[90] Currently, there are no sensitive markers of disease activity that can accurately capture the varying degrees of inflammatory activity in the setting of neurodegeneration. Due to the process of neurodegeneration and compartmentalized inflammation playing a key role in PMS, drugs with predominantly systemic anti-inflammatory activity are less likely to be effective, especially in older patients where inflammatory activity has declined.

There is a heightened focus on clinical trials for PMS. Recently, The European Committee for Treatment and Research in MS (ECTRIMS) in association with the International Progressive MS Alliance held a workshop to address strategies for the advancement of trial design in PMS.[91,92] The workshop addressed multiple aspects of trials for PMS and proceedings were published as a series of review articles in a themed issue of the *Multiple Sclerosis Journal*. The group recognized the growing importance of people with PMS in providing feedback and marketing and even in the design of trials.[93] Patients now undertake a larger role than just participating in volunteer trials. They are involved in providing feedback in developing more clinically meaningful outcome measurements, advocating financial support, and serving as representatives in the trial's development committees.

The group recognized the pathophysiology of PMS as playing a key role in the trial design and therapy selection. The pathophysiology of PMS differs from RRMS in which systemic inflammation progresses to compartmentalized inflammation and neurodegeneration. The dynamic changes in pathophysiology over the course of the disease highlights the importance of identifying the disease stage and timing of intervention. Drugs with anti-inflammatory properties will have more benefit in patients with active inflammation and are less effective in patients who have reached the late stages of neurodegeneration.[94] Enrollment of patients who have more active disease progression will likely have a greater sensitivity in detecting the treatments measuring progression than patients who do not progress. However, too narrow inclusion criteria will compromise the external validity and generalizability of results. More research to understand the pathophysiology and population characteristics of PMS are underway.

Due to a current lack of early and sensitive measurements of disease progression in PMS, an emphasis was placed on outcome measures. Clinical outcome measures such as the EDSS continue to serve as the established benchmark in PMS trials, but the shortcomings of EDSS limit its use alone as a sufficient outcome because of its near exclusive reliance in its upper ranges on walking and ignoring important functions such as cognitive and arm functions. Other measures have begun to surface that assess the vital clinical components of PMS. Together, these outcome measures address multiple facets of the clinical experience and are shaping trials to include a reworking and integration of new metrics such as composite measurements, cognition, and PROs.[95] The lack of a sensitive phase II trial outcome measure poses a limit to the timely advancement of potential therapeutic agents beyond their proof-of-concept phase. This contrasts with phase II trials for RRMS that employ focal MRI lesions to detect short-term changes. Currently, whole brain atrophy is the most accepted phase II outcome measurement in PMS.[96] However, there are notable limitations including slowness to change, inter-patient variability, and unidimensional measurement. Other biomarkers in development and testing, such as NFL, have begun to show promise.[97]

Despite challenges in PMS trials, there is progress in recent trials that have shown a positive effect in PMS including simvastatin,[98] biotin,[99] ocrelizumab,[89] and siponimod.[39] Potential evolution in the trials in PMS will focus on identifying agents targeting neuroprotection and remyelination, carefully identifying a study population with regards to baseline inflammatory activity, choosing accurate and sensitive outcome measures in both phase II and III trials, and exploring the potential of adaptive designs.

Conclusion

The past 25 years have witnessed substantial developments in the treatment of MS. Advancements in therapeutic agents are a direct result of clinical trials that demonstrated their efficacy. Just as the disease course has been redefined with the advent of DMTs, so have characteristics of trials that continue to test new agents. The present-day MS trial population no longer shares the same baseline characteristics as historical groups and is distinguished by earlier diagnosis and milder disease presentation due to increased availability of treatment. This change is present even in placebo groups, thus complicating the comparison of data across trials. At the same time, active comparator designs have replaced placebo-controlled trials for RRMS, as the latter is no longer ethical in an era of proven therapeutic options. The head-to-head comparison of two agents has increased the required trial sample size and duration to be able to detect significant on-study differences. This has motivated consideration of more efficient study designs such as adaptive designs that have the potential to seamlessly transition from phase II to phase III trials, thus reducing the cost and expediting the trial process.

At the same time, new options for clinical and neuroimaging outcome measurements are beginning to see use in trials to capture different aspects of the disease process. While traditional measures of relapse (e.g. changes in EDSS and focal MRI lesions) continue to remain the standard of assessment of disease activity, new parameters such as brain volume, PROs, MTR, OCT, NFL have contributed new dimensions to capturing disease progression.

Amidst the successful development of DMTs for RRMS, increasing focus has turned towards clinical trials for PMS where current therapies are limited and much needed. Experience with PMS trials has identified challenges in study design inherent in the nebulous characterization of the disease course and lack of sensitive measurements of disease progression. Unlike in RRMS where inflammatory activity can be assessed by relapses and lesion changes on MRI, there is no sensitive equivalent in measuring neurodegeneration and compartmentalized inflammation, which constitutes significant mechanisms in the pathophysiology of PMS. Nevertheless, recent research has shown positive results in multiple agents for the treatment of PMS, and outcome measures such as brain atrophy is an acceptable metric of neurodegeneration. Various agents in remyelination and neuroprotection are currently being tested, and the potential applications of adaptive designs are being explored.

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