INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2022, Volume 56, no. 3, pages: 228–235
DOI: 10.5603/PJNNS.a2022.0041

ISSN: 0028-3843, e-ISSN: 1897-4260

LEADING TOPIC

Leading Topic Editor: Alicja Kalinowska-Łyszczarz, MD, PhD, Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, Poland

Clinical trials in multiple sclerosis: past, present, and future

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ABSTRACT

For the past four decades, multiple sclerosis (MS) has been a focus for clinical trial development and execution. Advances in translational neuroimmunology have led to the development of effective disease-modifying therapies (DMTs) that greatly benefit patients with MS and mitigate their burden of disease. These achievements also stem from continued progress made in the definition and discovery of sensitive disease diagnostic criteria, objective disability assessment scales, precise imaging techniques, and disease-specific biomarkers. As a result, our knowledge of MS pathophysiology is more mature; the established clinical practice for the diagnosis and management of MS could serve as a roadmap to guide the development of more disease-specific interventions. In this article we briefly review the main achievements in the evolution of clinical trials for MS, and discuss opportunities for improvements.

Key words: multiple sclerosis, clinical trials, pharmacology

(*Neurol Neurochir Pol 2022; 56 (3): 228–235*)

Introduction

The widespread use of today disease-modifying therapies (DMTs) as the mainstay of treatment in multiple sclerosis (MS) draws on data provided by clinical trials over the past two decades. In parallel with the rapidly growing treatment landscape for MS, clinical trials have evolved to incorporate innovative designs and mechanistic insights [1]. Revised diagnostic criteria and the characterisation of MS phenotypes across the age range have improved MS pharmacotherapy trials [2, 3]. Today, MS trials benefit from sensitive diagnostic criteria and clinically relevant follow-up data permitted by the latest imaging techniques and objective disability progression documentation i.e. the expanded disability status scale (EDSS). Furthermore, new frontiers in para-clinical exams provide a growing list of biomarkers, some of which might hold potential biological significance.

All currently approved DMTs diminish two types of disease activity: the occurrence of inflammatory signal changes on magnetic resonance imaging (MRI); and the frequency of clinical relapses. MS trials can now consider potential pathophysiological differences between active and non-active disease, and recruit patients into prospective trials accordingly.

MS is a clinically, radiologically and pathologically heterogeneous condition. Treatment with various DMTs with different mechanisms of action (MOA) further differentiates patients with MS. This introduces statistical and ethical challenges to future trials. For instance, rather than placebo, novel treatments are likely to be compared to approved effective control DMTs, which might affect estimates of the magnitude of treatment effect and subsequently the success rate of the future trial. As the global cohort of patients diagnosed with MS reach advanced ages, they can be expected to transition to secondary progressive non-active MS. Regrettably, in spite

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Received: 06.03.2022; Accepted: 24.05.2022; Early publication date: 17.06.2022

of all their success in treating active MS, current DMTs have failed to provide meaningful clinical benefit for older patients living with progressive non-active MS. Here, we discuss how trials have evolved and contributed to the current state of clinical practice and research in MS.

Milestones in evolution of MS trials

MS diagnosis

Consistency in patient recruitment for trials depends on a consensus regarding diagnostic criteria. Optimal trial design in MS requires the appreciation of differences that distinguish MS subtypes. Originally, clinical disease course was adopted as a mean to categorise these subtypes and unify trials efforts in early studies.

Charcot's triad utilised nystagmus, intention tremor, and scanning speech in an initial attempt to define MS [4, 5]. In hindsight, this approach probably described patients with a preponderance of demyelinating lesions in specific locations of the central nervous system (CNS) such as the cerebellum, rather than an actual subset which holds any relevance for guiding clinical trial design and tailored treatment development. Historical MS diagnostic criteria, such as Schumacher's, defined the disease as an inflammatory disorder of the CNS with dissemination in time and space [6]. This was later expanded by Poser to address data driven from cerebrospinal fluid (CSF) and imaging components [7]. Eventually, it was the McDonald criteria that incorporated clinical aspects, MRI data and CSF oligoclonal bands to further simplify MS diagnosis. Revisions to the original McDonald criteria included gadolinium (Gd) enhancing lesions as a correlate of dissemination in time, and the co-existence of periventricular, juxtacortical, infratentorial or spinal cord lesions as a correlate of dissemination in space [8]. The diagnostic sensitivity of subsequently revised criteria was even further enhanced by considering patients presenting with clinically isolated syndrome (CIS) as definite MS, when MRI and CSF finding corroborated the diagnosis [9–14]. This increase in diagnostic sensitivity facilitated the recruitment of patients into potential trials. Currently, the approved criteria allow for a definite MS diagnosis within a single time frame pertinent to a typical demyelinating event, without waiting for a second attack.

Inadvertently earlier enrollment of patients during the course of the disease can artificially improve prognosis, due to lead-time bias. This is especially important when drawing comparisons involving historical trials in a fast-evolving paradigm like DMTs in MS. Under the 2001 and 2017 McDonald criteria, within 12 months of presentation, 50% of patients with CIS proceeded to definite MS. But based on the Poser criteria, only a 20% conversion rate to definite MS diagnosis was observed, underlining the sensitivity of the McDonald criteria [15]. It is difficult to ascertain to what extent the current perceived improvement in patients' clinical status is attributable to an expedited diagnosis, independent of DMT effect. Compared to historical cohorts of people with MS, modern MS cohorts, on average, have a lower annualised relapse rate (ARR) and a milder course of disease [16]. In fact, even patients in the placebo groups are experiencing longer relapse-free durations following their enrollments in trials; however, this is not as pronounced compared to DMT-treated patients who show statistically significant improvement in tangible clinical outcomes [2, 16].

More empirical evidence is urgently required in order to precisely calculate the extent of lead-time bias in the overall improved outcome of patients with MS receiving second or third generation DMTs. The TRaditional versus Early Aggressive Therapy for MS (TREAT-MS) trial is a randomised controlled trial that aims to: (A) evaluate, jointly and independently among patients deemed at higher risk vs lower risk for disability accumulation, whether an early therapeutic intervention considered highly effective versus a first-generation agent impacts the medium-term risk of disability; and (B) assess if, among patients deemed at lower risk for disability who start on first-line MS agents but experience breakthrough disease, those who switch to a higher-efficacy intervention versus a new first-line therapy have a different medium-term risk of disability (ClinicalTrials.gov/NCT03500328).

Regarding progressive MS, trials so far have used incongruous inclusion criteria to enroll patients. This lack of consistency has diminished the quality of pertinent trials for meta-analytical purposes. An objective definition of non-active progressive MS is crucial for trials that specifically seek to evaluate DMT efficacy in primary and secondary progressive MS phenotypes [17]. Building on the diagnostic acumen provided by the McDonald criteria, the 2013 Lublin consensus criteria drawn up by a panel of experts ratified a more precise definition for active vs. non-active disease and drew distinctions between relapsing, worsening, and progressive MS, thus paving the way for consistency in related trials [18]. Current methods in trials involving active relapsing MS allows for reliable appreciation of correlations between measures of disease activity and response to novel DMTs. Once prospective trials for non-active progressive MS achieve the recruitment of homogenous participants, similar novel objective measures may be developed to allow the evaluation of potential therapeutics.

Disability assessment in MS

The earliest therapeutic attempts to alter the disease course in MS by controlling inflammation were performed by Miller et al. and later by Rose et al., via the administration of adrenocorticotropic hormone (ACTH) or a saline placebo in patients believed to have had an acute clinical relapse [19, 20]. These studies implemented seemingly identical interventions; however, the outcome measures were fundamentally different. While Miller et al. measured treatment efficacy through subjective reports of improvement during follow up interviews, Rose et al. derived an objective assessment of improvement through neurological disability status scales [21]. Subsequent

longitudinal data challenged the treatment intervention in both these trials, since adopting long-term monotherapy with corticosteroids eventually proved ineffective in MS management [22]. However, the implementation of the disability scale used in the latter approach grew to become a pillar of clinical data appraisal for MS trials involving treatment efficacy.

The move to define disability as an objective disease outcome started with the works of Arkin et al. [23, 24]. A diverse neurological scale was originally suggested, and this was later simplified by Kurtzke into a 10-point disability scale [21]. The new scale could track clinical status in patients with MS and gave uniform and reproducible results. The introduction of half points further refined this tool; the expanded disability status scale (EDSS) is used today by all MS clinicians to assess disability in patients with MS. Alternatively, the MS functional composite (MSFC) for assessment of disability in MS was later developed to mitigate the inherent shortcomings of the EDSS including its over-dependence on bipedal ambulation, its lack of sensitivity to cognitive decline, and its non-linearity [25]. MSFC successfully registered arm function, dexterity, and cognitive capacity on top of ambulation. MSFC was criticised for the learning phenomenon during paced auditory serial addition test (PASAT). MSFC utilises z-scores to depict deviation from a reference population, and this might have contributed to its failure to replace the easily available EDSS as the standard assessment tool in MS clinical trials.

The term 'no evidence of disease activity' (NEDA) was introduced in 2013 to clinical practice and research into MS [26]. It describes a disease-free status as a surrogate marker for treatment response in patients with MS. The early NEDA criteria comprised data pertaining to relapse rate, new or enlarging T2 lesions or Gd-enhancing lesions, as well as confirmed disability worsening as measured by EDSS. To capture more subtle disease-mediated insults and pertinent treatment effects, the original NEDA criteria have since been updated several times. NEDA-4 expanded on its predecessor by including brain atrophy. Higher domain NEDA status later incorporated the use of neurofilament light chain (NfL) levels in CSF as a close correlate of ongoing axonal injury [27]. The NEDA criteria encapsulate an expanding yet granular view of MS disease activity. Previous studies have commented on the prognostic value of NEDA for future disability accumulation [28]. It is conceivable that NEDA could be employed independently as a holistic outcome measure in future DMT trials.

CNS imaging in MS

Prior to the age of MRI, computed tomography (CT) scans were the only option for investigating CNS structural attributes in neurological disorders including MS. Naturally, CT scans were ill-equipped to record many therapeutically relevant structural changes recognised today in MS patients. At best, CT scans could register contrast enhancing lesions, originally correlated with an active disease; these lesions appeared to be resolved on subsequent CT scans after short steroid regimens [29].

The advent of MRI permitted a leap forward in the appreciation of structural changes pertinent to disease activity that were detectable through imaging. This also provided a revolutionary advantage for MS trials [30]. As one of the earliest effective DMTs, interferon β-1b (IFNβ-1b) injection was successfully attempted by Paty et al. as an intervention for MS treatment between 1988 and 1993. Demonstration of IFNβ1-b's clinical success was greatly augmented by the evidence provided through MRI technology. MRI data proved that besides a better clinical outcome, treatment with IFNβ-1b significantly reduced the number of new and Gd enhancing lesions.

These results for the first time tied the MS imaging data to the approval of a novel therapy, setting a precedent for MRI as a reliable outcome measure in MS trials [31]. Today new Gd enhancing lesions, along with new or enlarging T2-lesions on MRI, are associated with immunologically active disease. Brain and spinal cord atrophy has been shown to correlate with disability progression [32, 33].

Advanced imaging techniques provide better resolution and precision; for instance, diffusion tensor imaging and magnetic resonance spectroscopy have been able to confirm disease activity beyond MRI lesion borders and within normal-appearing CNS tissues [34]. Similarly, seven-Tesla MRI has shown how conventional MRI studies might have underestimated the true MS lesion burden, especially in cortical grey matter [35]. Much like the leap that took place when MRI replaced CT scans, advanced imaging techniques may shine a light on new measures of disease activity and provide further therapeutic targets for future trials. Of note is the volumetric analysis of the choroid plexus; this immunologically-sensitive organ closely tracks the biological events pertinent to CSF and exhibits volume alterations relative to both MS disease activity and type of DMT [36, 37], and the identification and longitudinal assessment of chronic active MS lesions, also termed 'smouldering lesions' with paramagnetic rims [38–41].

DMT mechanism of action

The earliest clinical interventions in MS treatment trials depict the consensus on the disease pathophysiology; namely, acute inflammation drives MS activity which warrants treatment with corticosteroids or their agonists (i.e. ACTH) [19, 20]. Corticosteroids have been employed as treatment during active MS relapses as an attempt to mitigate organ damage [42], although longitudinal observations have not supported meaningful benefits to patients' long term clinical prognosis [22, 43, 44].

In contrast, data generated during IFNβ-1b trials showed a clinically meaningful benefit of IFNβ-1b treatment and affirmed IFNβ-1b as the first DMT approved for MS [45]. The validating study did also speculate about possible MOAs for the favourable results seen with IFNβ-1b therapy. Specifically,

interferon gamma (IFNγ) antagonism, suppression of immune response via suppressor T cells, and reduction in antigen presentation capacity of antigen presenting cells were suggested [46, 47]. To date, the exact MOA for IFNβ-1b in MS treatment remains controversial; however, this benchmark study cemented the paradigm that immunomodulation may prove favourable for MS, paving the way towards the development of other DMTs [48–50]. In fact, subsequent introduction of monoclonal antibodies as highly effective DMTs provided evidence for target-specificity against immunological cell subsets in relation to MS pathogenesis [51, 52]; furthermore, traffic-inhibiting agents suggested compartment-specificity of immunological events in relation to CNS autoimmunity. Natalizumab in particular showed how the access of encephalithogenic cells across the blood-brain barrier is a crucial step for disease establishment and ongoing activity [53–55]. Moreover, the success of B cell depleting therapies implied involvement of B cells in disease pathogenesis [56–58].

Future novel therapies will have to outperform the current DMTs, therefore facing higher thresholds before they are adopted into routine clinical care. Nonetheless, these thresholds should and will revolve around unexplored MOAs that may prove relevant in relation to MS activity and progression, in particular in relation to non-active progressive MS, where most DMTs have failed. While studies on ocrelizumab for primary progressive MS and on siponimod for secondary progressive MS have suggested relative efficacies compared to placebo, it is likely that the observed efficacies were driven by a minority of enrolled patients with active disease [17, 59–61]. Future trials in progressive MS may prioritise neuroprotection, regeneration, and remyelination as their primary goal.

Trial designs

As stated before, more sensitive diagnostic criteria, along with the availability of treatments with proven clinical benefits, have complicated future MS trial design. Earlier diagnosis and aggressive treatment strategies have significantly benefited MS patients and reduced the overall disease activity in MS cohorts. In current trials, unexpected disease activity may warrant rescue therapies with available effective DMT, diminishing the overall ARR of the respective cohort. In contrast, disproportionate enrollment of refractory MS phenotypes, i.e. non-responders to current DMTs in trials for new candidate therapies, might artificially deflate the potential efficacy of such therapies. Evidently, a head-to-head comparison of all available DMTs in randomised clinical trials is logistically and ethically impossible. As a result, MS trial designs over time have adopted changes in order to address some of these constraints.

Trials for the earliest DMTs, which enrolled placebo-treated controls, had clinical and statistical significance of effects being established against virtually no modification to natural disease course. IFNβ-1b and glatiramer acetate were each approved in such double-blind randomised placebo-controlled trials [45, 48]. A plethora of evidence attests to the detrimental consequences of delays in MS treatment, and therefore a generic placebo-controlled approach in MS trial design was deemed no longer ethical by an international task force in 2000 and 2008 [62, 63]. However, it recognised certain conditions that could allow for the use of placebo in trials. These conditions included patient refusal of available treatments, treatment failure, or regional unavailability of other treatments. In fact, teriflunomide, dimethyl fumarate, and fingolimod were all approved in comparison to placebo arms in spite of available and approved DMTs [64]. Considering the weight of evidence behind the pivotal role of early treatment in MS, the phase III trial for peginterferon β1-a was perhaps the last conservable account for placebo-controlled MS trials [65]. The dynamic nature of MS pathophysiology, specifically in response to different treatments, backs the rationale for placebo-controlled trials. Alemtuzumab, a highly effective DMT, was approved in 2014 without any comparison to placebo, setting a precedent for future novel therapies [66, 67]. Different classes of DMTs, including anti-CD20 B cell depleting agents, ocrelizumab and ofatumumab, as well as ozanimod, a sphingosine-1 phosphate receptor modulator, were all approved in trials with active comparator controls, confirming the feasibility of such a design in trials of new MS therapeutics [58, 68, 69]. Given the range of currently effective DMTs, one could argue that cessation of placebo-controlled trials is in fact in the best interest of MS patients. Any new DMT that is validated in an active-comparator design outperforms the benchmark for treatment efficacy. However, this very mechanism also requires the said trials to recruit larger sample cohorts, rendering them more costly to perform. Similarly, other designs such as combination trials may entail the recruitment of large sample sizes and longer follow ups before any meaningful synergistic benefits are detectable; however, within a select subset of therapies with complementary MOAs, DMT synergism may be interrogated in phase IV open label studies with relatively small samples (Clinical trials.gov/ NCT03135249, NCT04178005).

Outlook for MS clinical trials

Traditionally, MRI-based outcome measures and disability scales have proven useful in establishing DMT efficacy in trials. Their usefulness, however, is challenged by the ever-expanding scope of current and future trials. The downside to these outcome measures is twofold. First, they require the enrollment of very large patient cohorts, something which has become increasingly difficult with the availability of effective approved DMTs.

Second, many of the pathophysiological events pertinent to MS activity and progression do not reach their detection threshold. In fact, the hesitance of regulatory authorities, clinicians and researchers to adopt more sensitive and efficient measures is primarily because of the unavailability of alternative established reproducible measures with clinical relevance.

A major barrier specific to MS is the lack of representative biomarkers. Trials in the context of other conditions rely on such biomarkers as seen in the case of treatment development for cancer [70]. Disease-specific biomarkers would permit objective classification algorithms for diagnostic purposes as well, contributing to homogenisation of recruited samples in validating trials.

The main culprit behind MS, i.e. the immune system, is a dynamic entity; therefore a representative biomarker in MS, with reliable diagnostic and prognostic values to replace clinical correlates, is likely to prove elusive.

Efforts have been made to enhance the data gleaned from current imaging techniques. For instance, MRI-derived lesion load and brain atrophy sensitively measure current and past disease activity and facilitate an expedited transition to phase III trials for promising candidates [71]. The evolving imaging paradigms now attribute more weight to regional atrophy in CNS areas that are more sensitive to change and have better prognostic power including grey matter, thalamus and cerebellum [72, 73]. Optical coherence topography has seen an interest in trials to assess treatment efficacy as thinning of the retinal nerve fibre layer correlates to axonal injury [74]. Trials involving non-active progressive MS in particular might benefit from further validation of such methods. Non-traditional trial designs, such as multi-arm multistage adaptive trials or recruiting from biomarker-driven MS endophenotypes, to maximise the potential for response to new treatments, may further facilitate the validation of effective therapies in progressive MS [75, 76].

Biological fluid biomarkers are ideal outcome measures for trial purposes and patient follow up. Among the many nominees for a potential fluid biomarker in MS, so far only NFL has produced promising results in terms of correlation with ongoing neuroaxonal injury in patients with MS. Specifically, it has been shown to correlate with relapse incidence, EDSS scores, MRI lesion load, and brain or spinal cord atrophy [77–79]. NFL is especially interesting since its plasma levels correlate with its CSF levels, allowing for less invasive measures; however as a sensitive measure, NFL plasma level is prone to MS-independent fluctuations. Prospective multicentre studies are required before NFL is widely adopted by clinicians and MS researchers.

In conclusion, the evolving discovery and validation of DMTs in MS clinical trials have provided an array of therapeutics that have improved clinical outcomes and quality of life for patients with MS. Current achievements in disease diagnosis and detection of disease activity, along with a better understanding of the mechanisms underpinning the disease pathogenesis, have broadened the horizon for therapeutic possibilities. The future may well lie in biomarker-based individualised pharmacotherapy.

Conflict of interest: *None.*
Funding: *None.*

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