PEER REVIEWED

Challenges of Drug Development in Progressive Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterised by focal confluent lesions of primary demyelination followed by diffuse axonal damage and neurodegeneration in the entire CNS. Disease onset and clinical course are highly variable and mostly unpredictable. In the majority of patients (about 80%) the disease starts in the third decade of life with a relapsing and remitting clinical course, characterised by episodes of acute exacerbation followed by complete or partial recovery. These relapses are believed to be the consequences of focal inflammatory demyelinating lesions, the histopathological hallmark of MS. On average, after 10–15 years the disease converts into a course of slow progression (secondary progressive multiple sclerosis – SPMS). It seems that time to progression is independent of the number of relapses experienced after the first two years of disease[1].

Only about 15% of patients develop primary progressive multiple sclerosis (PPMS) characterised by continuous worsening without distinct relapses. The onset of PPMS is typically about 10–15 years later than relapsing remitting multiple sclerosis (RRMS) but at a similar age when the conversion to secondary progressive multiple sclerosis (SPMS) occurs[2]. It is not clear whether PPMS is a distinct disease entity or whether it just represents part of the variable clinical disease spectrum. If we assume MS as a primary inflammatory disease, in which demyelination and tissue injury is driven by immune-mediated mechanisms throughout all different stages and in all different courses, PPMS would be just a clinical variant of a common disease process[3]. However, if MS is a primary neurodegenerative disease, which is modified and amplified by the inflammatory process, PPMS could reflect the primary disease process of MS, and the other courses (RRMS and SPMS) are those modified by an inflammatory reaction[4].

Regardless of substantial difference between RRMS and progressive (secondary or primary) multiple sclerosis (PMS), evidence of subclinical disease activity defined by the presence of new focal contrast enhancing lesions at the brain MRI, typical for RRMS, can be present in patients with SPMS as well as PPMS. For this reason, it has been suggested to classify MS patients who have entered the progressive disease stage into those with or without evidence of disease activity and with or without disease progression[5]. The progressive phase of MS is characterised by diffuse white (WM) abnormalities, atrophy and cortical demyelination[1]. Clinical disease severity and the speed of disease progression are very variable between patients, but on average the speed of progression is similar between patients with PPMS and SPMS and is independent of the severity of previous relapses. The predicted average EDSS progression on ambulatory patients based on the linear mixed effects model in PPMS and SPMS are similar, at about 0.25 points per year[6–7], although it depends on EDSS entry level[8].

Diagnosis of progressive MS is a clinical judgment, with no gold standard diagnostic test. It is based on patient-reported clinical history and should be confirmed based on objective physical examination findings. Based on the 2017 McDonald diagnostic criteria, PPMS can be diagnosed in patients with a one-year history of disability progression, which can be retrospectively or prospectively determined, independent of clinical relapses, plus two of the following criteria: (1) One or more T2 lesions characteristic of MS in one or more typical brain regions (periventricular, cortical or juxtacortical, infratentorial); (2) two or more T2 lesions in the spinal cord, and; (3) the presence of CSF-specific oligoclonal bands. Providing a clinical definition of disease progression, might be difficult. Progression is characterised by a steady increase in neurological disability occurring independently of relapses. Diagnosis can be difficult to establish at disease onset (PPMS) and may go unrecognised by patients or physicians for some time. Exact date of progression onset is difficult to establish and is usually estimated retrospectively, once duration of continuous neurological worsening can be calculated[9]. Symptoms often fluctuate (pseudo relapses), although superimposed typical relapses might occur. Careful and detailed history-taking is key in differentiating events suggestive of disease activity from worsening of previously experienced symptoms. PPMS is defined by a progressive course from onset and SPMS by a progressive course following an initial relapsing–remitting course.

Possible Treatment Targets in PMS

The absence of suitable animal models for PMS makes it difficult to ascertain the reliable selection of therapeutic approaches in humans. Moreover, in the light of uncompleted understanding of PMS pathophysiology, possible treatment strategy to ameliorate progression could generally include protection of cellular elements against degeneration, and/or promotion of repair (remyelinisation). Because microglial activation, including the frequent presence of microglial nodules in the brain is a prominent feature of PMS[10], the use of drugs that enter the CNS and inhibit microglial activity might be one of the therapeutic options. Additionally, neuroprotective strategies to inhibit oxidative damage or induce antioxidative cellular defence mechanisms; mitochondrial protection strategy and/or strategy that targets different ion channels should be considered as potential treatments of PMS.

A further potential approach to treatment of PMS is promotion of remyelination, as axons that are remyelinated in experimental models seem to be protected from degeneration, at least in the short term[11]. A number of approaches to support remyelination show promise in animal models and could be investigated in PMS.

Biomarkers in PMS

Biomarkers that are predictive of disability accumulation in PMS would be useful to monitor treatment effects. However, no biomarkers specific for

PMS are currently available. As axonal degeneration is prominent in this form of disease, brain atrophy and proteins that are released from degenerating axons into the cerebrospinal fluid (CSF) are of potential utility.

Brain atrophy accumulates in multiple sclerosis at a rate of 0.5–1% per year, two to three times more rapidly than in healthy subjects, and is generally thought to reflect neurodegeneration underlying relentless accumulation of disability in PMS[12]. Extensive demyelination of grey matter has been reported in patients with PMS and the cortex is thought to be a primary site of neurodegeneration[13]. Cortical atrophy is associated with both disability and cognitive function. Grey matter atrophy is more useful than white matter atrophy in the prediction of clinical disability and is, therefore, regarded as a good potential outcome for trials of PMS[14]. However, it is not totally established what measure of atrophy is most informative: whole-brain atrophy, white matter, or grey matter changes, or atrophy of specific regions (thalamus, corpus callosum, or cerebellum)[15].

To be a useful biomarker for Phase II studies, the change of brain volume should be detectable over a short period of time (within one year or less). Sample sizes needed to demonstrate 50% reduction with 90% power on whole-brain atrophy progression in subjects with RRMS have been estimated on 70 subjects per arm needed in a one-year trial[16], which is quite close to data obtained from PMS subpopulation[17]. To improve the sensitivity to change of atrophy measures, it has been proposed to focus on specific brain areas like deep grey matter (DGM) which are including thalamus caudate, putamen and globus pallidus, or individual brain structures such as the cervical spinal cord and the cerebellum, rather than on the whole brain, which presents with more marked volume changes over time in the PMS population. The high-resolution, retrospective 3T MRI study over one year in patients with PMS showed a statistically significant change in raw volume in the caudate nucleus and in the raw total DGM, whereas clinical disability (EDSS score) did not significantly change during the one-year observational period[18].

It has been proposed that the raw DGM atrophy may prove efficient as a short-term outcome for proof-of-concept therapeutic trials in PMS. A treatment trial for an intervention that would show a 50% reduction in DGM brain atrophy would require a sample size of 123 patients for a single-arm study (one-year run-in followed by one-year on-treatment). For a two-arm placebo-controlled one-year study, 242 patients would be required per arm[18]. However, if only raw caudate atrophy will be assessed, 183 patients per arm will be requested[18]. The recently reported study of thalamic atrophy in a mixed population of MS (RRMS, SPMS and Clinically Isolated Syndrome – CIS), showed the average thalamic volume reduction of 0.71% per year in MS subjects, versus 0.29% per year reduction in healthy controls[19]. For the maximal effect size (hypothetical treatment that could slow the rate of thalamic atrophy in MS to that of normal aging) in CIS and RRMS population with 80% power, 118 patients per arm will be needed[19].

In a cervical spinal cord study[17], the sample size to show a 30% treatment effect using the cervical spinal cord was estimated at 157 subjects per treatment arm utilising PPMS patients, but 1538 subjects per arm if an SPMS-only study population were enrolled. These results suggest that the cervical cord area is more sensitive to change in PPMS than in SPMS. As for the cerebellum, the sample size estimation indicates feasible studies: the numbers of patients required to detect a 30% treatment difference has been estimated to be 81 per arm for cerebellar volume and 162 per arm for cerebellar cortex volume (90% power, type 1 error alpha = 0.05)[20].

Several new outcomes, including diffusion tensor imaging (DTI), magnetic transfer ratio (MTR) and diffusion weight MRI imaging, have been considered for clinical trials PMS. The diffusion weight imaging has been proposed for the assessment of caudate and brainstem integrity, while MTR has been proposed as a marker of brain myelin content, including in the cerebral cortex. Optical coherence tomography (OCT, a non-invasive, quantitative, and low-cost imaging technique of the retina) showed high correlation with whole brain and grey matter atrophy and physical disability in subjects with PMS. It can serve as an outcome measure of axonal loss in proof-of-concept clinical trials in PMS[21].

CSF and serum biomarkers: The two most promising biomarker candidates for nervous system damage-related pathology in PMS are neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). Both of them can be detected in serum and they reflect their concentrations at cerebrospinal liquor (CSF). Higher serum concentrations of both GFAP and NfL were associated with higher EDSS, older age, longer disease duration, progressive disease course and MRI pathology[22]. GFAP, unlike NfL, is not increased in association with acute focal inflammation-related nervous system damage.

Clinical Outcome Measures in PMS Clinical Trials

EDSS: Almost all clinical studies of PMS have used Expanded Disability Status Scale (EDSS) assessment, as a primary clinical endpoint. Despite general acceptance of the EDSS, there are many limitations and caveats, which include high intra- and inter-observer variability particularly in the assessment of PMS, non-linearity (bimodal distribution) and lack of the assessment of several functional domains (cognition, upper arm function).

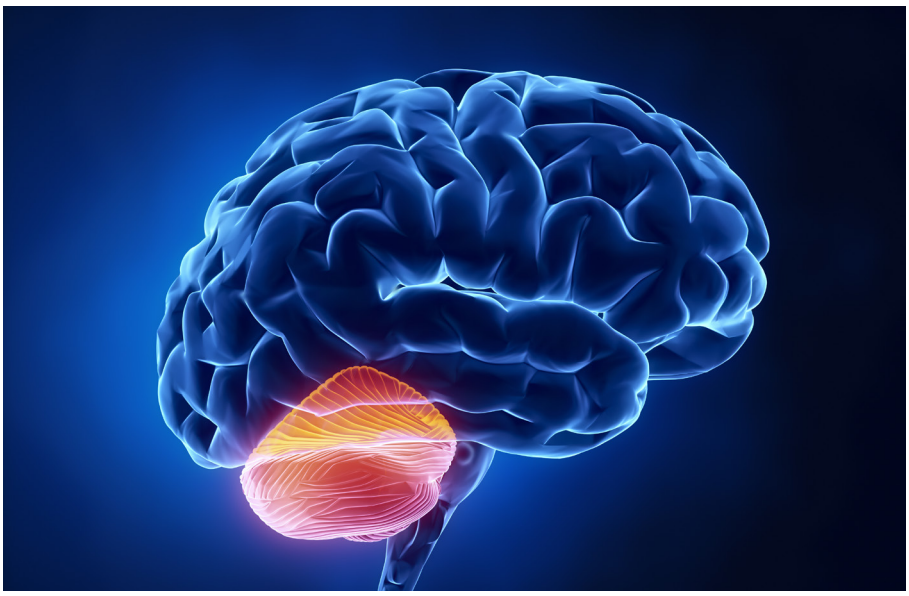
Because of the unequal distribution between EDSS steps, a change will be dependent not only on actual disease progression, but also on EDSS entry level. Responsiveness to EDSS is limited (i.e. arm paresis at EDSS 4 will make a change in the score, but not at the EDSS 5.5 or 6). Because the EDSS is an ordinal scale, non-parametric statistics should be used in statistical analysis. This implies that significant differences between groups can be calculated, but the magnitude of differences cannot. In line with this, results should not be presented with means and standard deviation, but with median values and interquartile ranges[23].

Although it is a well-recognised scale for neurologists, the EDSS is severely restricted as an outcome measure for trials in PMS[24]. Indeed, in PMS patients, EDSS is insensitive to all but the most relevant changes in ambulation, which usually are difficult to observe in the majority of PMS patients included in clinical trials due to a plateau effect at the EDSS 6. This problem was recognised early in PMS trials, and many studies were designed to use not only

the EDSS (and ambulation scores) but also other functional outcomes, such as hand dexterity[15]. Using this approach, a study with oral methotrexate showed improvement in PMS subjects with no change at EDSS[25].

Multiple Sclerosis Functional Composite (MSFC) was developed as a complementary outcome to EDSS, adding its ability to quantitatively probe not only ambulation but also cognition and hand dexterity. The MSFC has been shown to be a more sensitive measure of treatment efficacy than the EDSS in PMS[26], however, it is not widely accepted by regulatory agencies as a primary clinical outcome measure. The crucial issue with this method is the use of Z scores and the unknown clinical value of a change in the Z score with respect to a patient's actual function in the three domains tested. Moreover, comparison between Z scores across studies is difficult. MSFC includes the floor and ceiling effect in the cognitive domain test – PASAT-3, which is why the Symbol Digit Modalities Test (SDMT) has been suggested as a replacement. Several authors are recommending the low-contrast letter acuity test as an additional, fourth domain, to add to the MSFC. Regardless of its disadvantages, the MSFC may be used as the primary endpoint in future clinical trials if its components are applied in a sensible way[23].

Patient-reported outcome measure (PROM) is defined as 'any report of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'[27]. There is an increasing importance of PROM in PMS trials. There are several measures of health-related quality-of-life used in MS studies. PROMs that assess activities of daily living (ADL) are of particular value in PMS. They are able to demonstrate clinical relevance of MS-specific outcome measures. Unfortunately, there is no MS-specific ADL scale. The most frequently used global PROM in multiple sclerosis is the Multiple Sclerosis Impact Scale (MSIS) which has been correlated with clinical and imaging metrics specifically in progressive forms of the disease[28]. Limitations of PROMs include their unblinded nature and potential expectance bias. Also, questionnaires assessing quality of life are prone to being influenced by more than just disability[23].



	Phase II – exploratory	Phase III - confirmatory
Design	Randomised Double Blind Placebo Controlled Parallel	
Subjects	Age 16-65 years; PMS diagnosed by McDonald criteria 2017 Proven progression in EDSS 0.5 at least one year before baseline No clinical relapse within 24 months before baseline (SPMS) Current EDSS 3 (4) – 6.5 With or without disease-modifying treatment	
IP exposure	12 months	36 months
Sample size per arm	70-150	380
Primary efficacy tools	Whole brain atrophy; Focal brain atrophy; Spinal cord atrophy (PPMS)	EDSS (time to, or percentage of, clinically definite progression – CDP)
Secondary efficacy tools	EDSS; MSFC; OCT; PRO	MSFC four domains; Brain atrophy (whole or focal); PRO; OCT
CSF or serum biomarkers	Neurofilament light chain (NfL); glial fibrillary acidic protein (GFAP)	

Table 1. Outline of the study designs in progressive multiple sclerosis

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