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Personal Viewpoint

Inclusion criteria used in trials of people with progressive multiple sclerosis

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Introduction

The clinical phenotype 'progressive multiple sclerosis' (PMS) has commonly been divided into two subgroups, primary progressive multiple sclerosis (PPMS) characterised by progressive worsening of neurological function and secondary progressive multiple sclerosis (SPMS), where progressive neurological worsening occurs after an initially relapsing period (RMS) of variable duration.[1]

The complex pathophysiology of PMS creates challenges for the development of effective disease modifying treatments (DMT).[2] It is therefore not surprising that despite numerous trials, only ocrelizumab (Ocrevus®) has been licenced to date for PPMS.

However, the sensitivity of the outcome measures to treatment response, and the importance attributed to a specific functional system(s), are determinants of outcome and, hence, for 'the success' of a treatment.[3] Another important aspect is whether people with progressive multiple sclerosis (pwPMS) are likely to progress, or not, using these outcome measures, in the defined period of the trial. As recent disease progression predicts further disease progression,[4] some trials require evidence of disease progression for a defined period of time prior to screening. We hypothesise that these aspects of trial design in progressive MS are crucial to the potential success of clinical trials.

We conducted a review of the inclusion criteria used in trials for pwPMS over the last 20 years, as a framework to potentially improve the design of future DMT trials in this population.

The aim of this paper was to identify and analyse the inclusion criteria used by industry-sponsored and/or investigator-led trials to recruit pwPMS into clinical trials of DMTs in order to show the absence of consensus concerning their current use and suggest the use of assessments tools such as 9-Hole-Peg-Test (9HPT), and 25-foot walking (T25FW) to better characterise PMS population.

Methods

A systematic literature search was conducted in March 2017 using the search term 'randomized progressive multiple sclerosis trials' applied to PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), ClinicalTrials.gov database (https://clinicaltrials.gov/), EU clinical trials (https://eudract.ema.europa.eu/), Cochrane Central Register of Controlled Trials (CENTRAL; http://www.cochranelibrary.com/about/central-landing-page.html) and the International Standard Randomised Controlled Trial Number (ISRCTN; https://www.isrctn.com/) register. Only randomised double- or single-blinded trials involving people with PPMS and/or SPMS were included.

Results

Selection criteria

A total of $n = 112$ randomised trials were included (see Supplementary Material). Seven were phase I, 8 were phases I–II, 47 were phase II, 7 were phases II–III, 23 were phase III, 2 were phase IV and 18 were not defined. Five inclusion criteria were identified as key for patient selection: age, Expanded Disability Status

Scale (EDSS), disease duration, MS subtype and evidence of disease progression.

Age

A total of 96 trials had age as one of their inclusion criteria. The majority of trials (76/112) had a minimum age defined, usually the minimum age of legal capacity. Six trials focused on a slightly older population with a minimum age of 30–45 years.

EDSS

Out of the 112 selected trials, only 21 did not require a specific EDSS range and included EDSS 0.0 up to 8.0. For the majority of remaining trials, the lower score was between 3.0 and 4.0; and the upper limit between 6.0 and 6.5. Only 25 trials accepted an EDSS above 6.5.

Disease duration

Forty-two trials required a minimal period of time between the disease onset and inclusion. This time lapse varied from a minimum of 6 months to 5 years. On the other hand, 11 trials set a maximal limit for disease duration from 5 to 20 years.

Type of MS

Forty-two trials included both people with PPMS and SPMS, while 39 out of 112 included only people with SPMS, 12 out of 112 included only people with PPMS. Finally, 19 trials included both relapsing-remitting multiple sclerosis (RRMS) and PMS patients.

Evidence of disease progression

Evidence of recent disease progression was required in 80 trials. Accepted evidence included the patient's clinical history (55%), documented EDSS worsening (38%) or changes on other indices such as the 9HPT and timed T25FW tests (17%).

No specific detail was provided concerning how clinical history of progression was assessed. For the 42 trials where EDSS worsening was required, progression should have occurred in a specified period of time (1–2 years before enrolment) and the last relapse should not have occurred, from 30 days to 2 years depending on the specific trial, before enrolment. The most common requirement was an increase of a minimum of 0.5 on the EDSS scale if the initial EDSS was larger than or equal to 6.0 or an increase in 1.0 point if the initial EDSS score was below 6.0. In addition, a time window was specified in most trials, typically a change was required over a period of 6, 12 or 24 months. Eighteen trials used the 9HPT, T25FW, the Symbol Digit Modalities Test (SDMT), functional system scores (FSS), ambulation index (AI) and Multiple Sclerosis Severity Score (MSSS) to define pre-study progression.

Results of trials

Of 112 trials, 9 had been stopped, 27 were still ongoing, 20 were completed but results not yet published in peer-reviewed journals and 56 had been published. Sixty-eight different compounds were investigated. Of the published trials, 32 did not meet their primary outcomes and 24 were either positive or showed a trends towards a positive result (Table 1).

Out of the 24 positive trials, only two used self-monitoring tools for pre-trial evidence of progression.

Discussion

The last 20 years have highlighted not only the difficulty of effectively treating, but also how to effectively measure relevant clinical changes in pwPMS. The lack of positive results and consequent dearth of licenced drugs could be due to many reasons such as the potency and/or the mechanisms of action of the therapy, the sample size, the duration of the trial or the level of inflammatory activity in the enrolled population.

The apparent lack of consensus concerning patient selection for PMS is clearly manifest from our analysis and highlighted by the variable definition and requirement of 'proof of recent disease progression', which is important to identify study subjects who would be informative for the trial outcome.

Interestingly, in trials using clinical history, the specific type of information needed was not well-defined and included various kinds of information ranging from a subjective self-assessment to an objective clinical examination described in the medical records.

Worsening of EDSS was the second most common (38%) element serving as evidence of progression. This underlines the importance of obtaining a regular EDSS as part of routine neurological care, in order to identify patients eligible for trials. Unfortunately, an EDSS assessment is time-consuming and not

Table 1. Phase II and phase III clinical trials with positive results.

Medication	Results	Phase	Number of patient (*N*)
PPMS			
Amiloride	Reduction of the rate of brain atrophy on MRI	II	14
Ocrelizumab	Lower rate of clinical and MRI progression	III	732
IVIG infusion	Delay disease progression	III	231
Linomide	Reduction of MRI activity	II	30
Rituximab	Reduction of disease progression in younger patients with active lesions on baseline MRI	III	439
SPMS			
T-cell vaccination	Clinical effect on relapses and on disability	II	26
Mitoxantrone	Reduced progression of disability and clinical exacerbations	III	194
Interferon beta-1b	Delays sustained neurological deterioration	III	718
Interferon beta-1a	Benefit on MSFC progression, relapses, quality of life and MRI activity	III	436
Antibodies against IFN-gamma	Reduced disease progression	III	45
Cyclophosphamide	Decreases the risk of progression	III	138
Pirfenidone	Positive effect on clinical disability and bladder function	II	43
Simvastatin	Reduction of the rate of brain atrophy on MRI	II	120
Autologous mesenchymal stem cell transplantation	Reduction of MRI activity/suggestive of neuroprotection	II	10
PPMS and SPMS			
Natalizumab	Reduced the inflammation level of intrathecal biomarkers	II	17
Fampridine	Mean improvement on the Multiple Sclerosis Walking Scale (MSWS-12)	II	635
Masitinib	Slight improvement using the MSFC	II	35
Methotrexate	Less progression of impairment for upper limbs function	II	60
Cladribine	Reduction of disease progression and MRI activity	II	51
Cyclosporine	Delay of progression of disability in a group of patients with moderately severe MS	III	547

SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; IVIG: intravenous immunoglobulin); IFN-gamma: interferon gamma; MRI: magnetic resonance imaging.

performed in many clinical settings. In addition, EDSS is arguably not the best outcome to evaluate disease progression, as it tends to focus on walking abilities, is non-linear and has ceiling and floor effects.[5] Finally, 18 trials required worsening of disability as assessed by patient using patient-related outcome measures (PROMS).

All these data illustrate a lack of homogeneity in inclusion criteria related to PMS trials. It is clear that the MS community has not reached consensus on what needs to be evaluated in people with multiple sclerosis (pwMS) to select an informative population for clinical trials.

Second, the evidence needed to confirm progression tends to be the same in the pre-trial and trial periods (see Table 2). There is also a lack of data on the defined sensitivity of established tests to measure pre-trial change in disability worsening. There is also no consensus about which tools to use and what constitutes a meaningful change in pre-trial disease worsening.

Reviewing previous trials, positive treatment effects were seen (Natalizumab (NCT01416181), Interferon,[6] Rituximab,[7] Methotrexate,[8] Cladribine[9]), but not on the primary outcome measures. It is possible that 'negative' trial outcomes are as much due to a size effect or to a lack of sensitivity to change of the

Table 2. Pre-study disability worsening and disability outcome measures on a trial-by-trial basis.

On-trial primary outcome							
		EDSS	Assessment tools	EDSS + assessment tools	None	Other (MRI)	
Pre-trial disability	History	8	3(*)	2	1	14	28
	EDSS	7(***)	1(*)	2(*)	0	2(*)	12
	Assessment tools	1(*)	3	0	0	0	4
	History + EDSS	6(****)	6(*)	1(*)	0	9 (**)	22
	History + assessment tools	3	1	1	0	2	7
	EDSS + assessment tools	0	1	0	0	2	3
	History + EDSS + assessment tools	4(*)	0	0	0	0	4
	None	7(**)	4(*)	1(*)	1	19(***)	32
		36	19	7	2	48	112

EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging.
(*) denotes the number of positive clinical trials.

primary outcome measures used as due to an absence of effect on disease deterioration.

Our review shows that EDSS remains the outcome measure in most progressive trials, despite evidence that it is not sufficiently sensitive to measure change in pwPMS.[5] We suggest that tools assessing functional systems with greater reserve capacity, which may allow detection of a treatment effect, should preferably be used.[10] However, the biological demonstration of a treatment effect may require more than a functional system assessment. In fact, some trials adopted composite outcome measures such as multiple sclerosis functional composite (MSFC) or EDSS + 9HPT that allow measuring change in pwPMS at EDSS of $\geqslant 6.5$ in combination with other primary outcomes.[11]

More responsive and meaningful outcome measures, for example, the 9HPT and PROMS, may also allow inclusion of people with more advanced MS, including those using wheelchairs, into clinical trials. We would also acknowledge that EDSS 6.5 does not mark a cliff edge beyond which the pathophysiology of MS suddenly changes to become an entirely non-inflammatory, neurodegenerative disease.[12]

In summary, this work showed both a high variability in inclusion criteria and also a lack of reporting standards. In order to improve the outcome of future trials in advanced MS, we propose the systematic use of the standard outcome measures used and also the inclusion of self-monitoring tools to better, and objectively, document disease worsening prior to trial entry and an effect on those measures. This may improve patient selection for PMS studies and hopefully exclude patients who are stable and hence are non-informative. Data collected as part of regular and continuous self-monitoring is a rich source of information to complement regular clinical assessment.[13] We are developing web applications (www.clinicspeak.com) which will hopefully allow patients to perform a web-EDSS, 9HPT,[14] T25FW and walking distance and to record change over time. Engaging patients in self-monitoring should improve recruitment and allow better tracking of disease progression using new outcome measures during trials.

Limitations

Publication bias is a major drawback of this review. Indeed, out of the 112 trials, 47 have no published results, which represents large amount of missing information. We highlight that 24 trials showed positive results. Twenty trials are reported as completed but results are not publicly available (January 2018). In the future, ClinicalTrials.gov development of new penalties for Responsible Parties who fail to comply with registration or results submission requirements will make it easier to analyse data as both entry criteria and results are now required.

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