CNS Drugs
DOI 10.1007/s40263-016-0340-9

REVIEW ARTICLE

Secondary Progressive Multiple Sclerosis: Definition and Measurement

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Abstract Secondary progressive multiple sclerosis (SPMS) is diagnosed retrospectively and involves a clinical course characterized by a progressive accumulation of neurological disability, independent of relapses, following an initial relapsing–remitting (RR) phase. Our incomplete understanding of the pathological mechanisms underlying neurodegeneration in multiple sclerosis (MS) may explain why, to date, there is no definitive imaging or laboratory test that is able to inform us when the disease is clearly entering into a progressive phase and why the vast majority of clinical trials testing immunosuppressant and immunomodulating drugs in SPMS patients has so far yielded disappointing or mixed results. Here we discuss the definition(s) of SPMS and how it may vary, outcome measurements (current and emerging) and modern trial design.

Key Points

The pathogenesis of secondary progressive multiple sclerosis is incompletely understood.

No definitive imaging or laboratory test exists that is able to inform us when the disease is progressive.

The goal of any proposed treatment for secondary progressive multiple sclerosis should be the prevention, delaying or slowing of the accumulation of disability.

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Published online: 11 May 2016

1 Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) [1] with a reported prevalence of between 1 in 500 and 1 in 1500 in Europe, North America and Australasia, and represents the commonest acquired disabling neurological disease affecting young adults in temperate latitudes.

MS usually starts with a relapsing–remitting (RR) clinical course, characterized by episodes of neurological dysfunction, called relapses, related to the development of lesions within the CNS [2]. The complete remission of the symptoms generally occurs during the early stages of the disease. However, in the majority of patients, after a variable period of time the disease enters into a phase of gradual progression of disability, termed secondary progressive (SP) MS. Although the nature of the symptoms and the duration of the RR phase are extremely variable, the accumulation of disability during the SP phase appears to be fairly constant in the majority of patients, regardless of the initial course [3]. In approximately 10–15 % of MS patients, the disease is characterized by a steady progression of neurological disability since the beginning, with a continuous irreversible increase of functional impairment over months to years, apart from minor fluctuations. These patients are diagnosed with primary progressive MS (PPMS) [4, 5].

SPMS has been traditionally considered to start at around 40 years of age [6], albeit recent studies have reported a higher age of onset [7, 8], and continues at a constant speed in the same patient. Several reasons could account for this dissimilarity among studies. Clinicians may be cautious or sometimes even reluctant to label patients as affected by SPMS due to the lack of disease-

modifying treatment for this stage of the disease. The diagnosis of SPMS may be further delayed by the fact that the initial signs of progression are often subtle and in the transition they may be unclear [8].

The patient's age at the first clinical attack is the factor most strongly associated with the time required for the transition towards the SP phase, as patients with a later onset generally take less time to enter into progression [9]. During the secondary progressive phase, it is still possible to have episodes of clinical worsening classifiable as disease relapses [10–13], although active contrast-enhancing lesions become less frequent in SPMS than during the early RR phase [14, 15]. The average time between the onset of the disease and the beginning of the SP phase is 19 years, although the variability is enormous [9, 16–19].

2 Definition of Secondary Progressive Multiple Sclerosis

After an international survey, in 1996 the definition of SPMS was standardized as an initial RR disease course followed by progression with or without occasional relapses, minor remissions and plateaus [20]. The recent 2013 revision [10] highlighted that SPMS is usually diagnosed retrospectively by a history of gradual worsening following the initial RR course, and that clinical, imaging (MRI), immunological or pathological criteria are needed in order to characterize the transition point when RRMS converts to SPMS. The meaning of disease progression, determined annually by history or objective measure of change of disability, has also been discussed [10]. The word 'progression' denotes the continuous worsening of neurological impairment, independent of relapses, over a period of at least 6 [21–23] or 12 months [10, 24]. Clinical progression is not uniform, but may plateau and be characterized by periods of relative stability [10, 20]. It is usually difficult to determine the precise moment of transition from the RR to the SP phase and this implies that clinicians usually diagnose SPMS retrospectively, after several years of documented continuous neurological worsening.

It is clear that the diagnosis of SPMS and its differentiation from PPMS, or indeed from other gradually progressive neurological disorders, can remain elusive, being based mainly on clinical judgment, without any fully reliable diagnostic test [25]. Particularly, the differential diagnosis between PPMS and SPMS is often based on a patient's ability to recall previous episodes of a neurological symptom, these being sometimes very mild and therefore overlooked [25]. Furthermore, it seems more sensible to assume that the sharp distinction between RRMS and SPMS is artificial and that the progression is likely to commence in the inflammatory RR stage.

3 Pathological Mechanisms Underlying Disease Progression

Whether SPMS is characterized by a prevalence of compartmentalized inflammation or neurodegeneration is still debated. Pathologically, it seems that inflammation does not stop in the progressive stage; conversely, it persists, at least within the CNS, behind a closed or repaired blood brain barrier [26–28], although some authors suggest that peripheral inflammation may also continue to play a significant role during the progressive phase [29–33]. Interestingly, meningeal inflammation has been characteristically described in SPMS and it has been hypothesized that it may play a role in the development of disability [34–36]. Lymphoid follicle-like structures have been described in post-mortem studies in about 40 % of all SPMS patients [37–39]. These follicle-like structures can be detected along the whole extension of the meninges, but are prevalent along and in the depth of the cerebral sulci [39] and may represent the phenotypic extreme of a continuum of meningeal inflammation characterizing MS pathology [40]. MS patients showing these follicle-like structures also had a higher level of cortical pathology with cortical lesions, cortical atrophy and subpial demyelination [39, 41]. One of the main possible explanations is that the infiltrating meningeal lymphocytes produce high levels of cytotoxic and pro-inflammatory cytokines in the cerebrospinal fluid (CSF) that may be responsible for the cortical damage, either directly or indirectly, probably through microglial activation [36]. Interestingly, the follicle-like structures are characterized by aggregates of CD20+ B lymphocytes dispersed in a reticulum of CD35+ and CXCL13+ stromal cells/follicular dendritic cells, and Ig+ plasmablasts/plasma cells [36, 37, 39, 42].

Pathological studies show that mitochondrial damage is another contributing feature associated with progression in MS [43]. Two major mechanisms have been proposed to explain the axonal damage related to mitochondrial dysfunction: one is nitric oxide-related and the other is glutamate-related. They cause alterations of ATP synthesis, permeability transition pore opening, release of proapoptotic factors, electron transport chain and ionic homeostasis dysfunction, all eventually leading to mitochondrial damage [43]. Moreover, in demyelinated axons, sodium channels become redistributed and their synthesis is upregulated [44], leading to unsustainable energy requirements and, ultimately, to the failure of Na+/K+ ATPase pumps to maintain ionic gradients [45, 46]. In the end, axons accumulate intracellular calcium and this event triggers many metabolic pathways leading to apoptosis [43].

Another aspect to consider in SPMS pathology is vascular dysfunction [47]. MS patients clearly have an

increased prevalence of vascular risk factors (also a function of age), such as reduced physical activity [48], high levels of homocysteine [49, 50] and smoking [47] and an increased risk of ischaemic stroke [51, 52] and venous thromboembolism [51]. Histopathological similarities have been highlighted comparing the so-called type 3 MS white matter lesions [53, 54] (characterized by selective loss of myelin-associated glycoprotein [MAG] and apoptotic-like oligodendrocyte changes) to acute white matter stroke [55] and likely endothelial dysfunction [56]. It has been hypothesized that the thrombotic manifestations in MS patients may be part of the activation of innate immunity [57, 58], linking together these two pathological aspects of the disease. Intriguingly, high-dose simvastatin (80 mg a day) has been recently demonstrated to reduce the progression of brain atrophy and to have a significant effect on clinical and patient markers of progression in a phase II trial in SPMS patients [59]. Statins have a protective mechanism on endothelial function [60] and a cell protective mechanism [61], with reduction of the release of free radicals [62] and prevention of glutamate-mediated excitotoxicity [63].

Therefore, in totality the neurodegeneration of progressive MS is a highly complex series of interlinked events and multiple factors can contribute.

4 Outcomes: Clinical, Imaging and Laboratory-Based

According to the European Medical Agency (EMA) guidelines [64], the goal of any proposed treatment for SPMS should be the prevention or delaying of the accumulation of disability. Ideally, clinical trials in SPMS should enrol patients without recent relapses and neuroradiological activity. Moreover, a steady progression, independent of clinical relapses, should be documented in the period immediately prior to enrolment. Relapse activity should also be recorded during the trial and reviewed when assessing the progression of disability during the trial [64].

One of the main explanations for the difficulties encountered in clinical trials in SPMS is the lack of easily reproducible and sensitive outcome measures. The available outcome measures for SPMS clinical trials can currently be grouped into clinical and imaging outcome measures [25]. Two key aspects should be considered in the choice of the ideal outcome measure for SPMS trials. First of all, it should be easily reproducible and sensitive to change in a relatively short time [25]. Secondly, it should reflect the pathology causing irreversible physical disability typical of disease progression (i.e. neuro-axonal damage and loss) [65]. An extensive review of all the possible outcome measures in SPMS is not the goal of this paper and can be found elsewhere [25, 66–68].

4.1 Clinical and Patient-Reported Measures

Measures of clinical outcome include the Expanded Disability Status Scale (EDSS) [69], Multiple Sclerosis Functional Composite (MSFC) [70, 71], cognitive measures and patient-reported outcomes [25].

The EDSS currently is the most widely used and traditional scale in MS clinical trials [64, 72]. It quantifies the level of clinical disability with a 20-point scale and explores eight functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral and other functions), by scoring the level of impairment of each of them. However, it has several well recognized limitations: steps 0 to 3.5 are defined by the functional systems impairments, whereas the steps between 4 and 7 are largely influenced by walking, and the highest steps are determined by the dependence of the patient for self-care, feeding and communication [73]. It follows that EDSS is an ordinal, nonlinear scale [74] with a high inter-rater variability [72] and an overemphasis on walking ability [25, 75, 76], especially for the range of disability typical of SPMS patients, minimizing, for example, cognition and upper extremity function [25]. Disability progression using EDSS in clinical trials is usually defined as a sustained increase of 0.5 or 1 point (usually confirmed at least for 3–6 months). A 1-point worsening for EDSS scores $\leq$5.5 and a 0.5-point worsening when baseline score is >5.5 seems widely accepted [64]. To increase the reliability of the EDSS, the EMA has proposed the following [64]: clinicians should receive specific training for EDSS; the same physician should evaluate the same patient during the trial; standardization of protocols for neurological examination; and there should be actual observed measurement of walking distances for assessments of mobility [64].

The MSFC was also designed to assess cognition and upper extremity function as well as walking ability [77]. It is obtained by calculating the *Z* scores of a timed 25-foot walking test, 9-hole peg test, and Paced Auditory Serial Addition Test (PASAT-3) [71]. The advantages include excellent inter-rater variability [78]; administration can be carried out by trained technicians as well as medical staff; and good correlation with EDSS [79], patient-reported outcomes [78, 79], and MRI measures [80, 81]. However, the clinical significance of a change in the value of Z scores over time is still unclear [25], and a sustained worsening of 15 or 20 % for the timed 25-foot walking test and 9-hole peg test are generally used [82, 83]. The replacement of the PASAT-3 with the Symbol Digit Modalities Test (SDMT) [84], and the addition of low-contrast letter acuity to

include a visual assessment [85], have been invoked as possible improvements.

The MSFC had rightly highlighted the need for a good and robust measure of cognition in clinical trials as approximately 45–60 % of all MS patients have a cognitive impairment [86, 87], and progressive MS patients experience cognitive difficulties more frequently and more severely than RRMS patients [88]. The Rao brief repeatable neuropsychological battery (BRNB) and the minimal assessment of cognitive function in MS (MACFIMS) represent the most used and validated cognitive assessments in MS patients [89]. The SDMT is included in both these batteries to assess visual processing speed and working memory and it has been demonstrated to be the most sensitive neuropsychological test across both batteries to detect cognitive impairment. It can be used to screen cognitive impairment [90] and may be able to identify transient cognitive relapses [91]. The SDMT, together with The California Verbal Learning Test –II [92] and The Brief Visuospatial Memory Test [93] make up the Brief International Assessment of Cognition for MS (BICAMS), recommended by an expert consensus committee of neurologists and neuropsychologists to assess cognitive impairment in MS [94]. BICAMS is optimized for small centres and can be administered by one or few staff members, who may not have specific neuropsychological training. Considering that cognitive impairment represents a relevant and difficult-to-assess clinical impairment in MS, and that clinical trial outcome measures need to take into account this aspect [95], BICAMS may be a reliable endpoint for clinical trials.

Finally, patient-reported outcome measures (PROMs) are assuming an increasingly important role in clinical trials [96], and MS-specific measures have been developed, such as the multiple sclerosis quality-of-life questionnaire (MSQoL-54) [97], functional assessment of multiple sclerosis (FAMS) [98], and multiple sclerosis impact scale (MSIS-29) [99, 100]. Another outcome tool, the Patient-Reported Indices for Multiple Sclerosis (PRIMUS) has recently been developed and has been demonstrated to correlate with perceived MS severity, general health and symptoms of depression [96].

4.2 Imaging

A major problem to overcome, particularly in phase II SPMS clinical trials, is the difficulty in detecting a significant change in clinical disability measured with the scales above, and therefore, the need to enrol a large number of patients to demonstrate effect (>1000 at phase III) and over a long trial duration (say 3 years). Imaging interim markers have been developed and are being evolved to allow quicker screening of potential therapeutic compounds [25]. Ideally, a valid imaging biomarker should be not only highly reproducible and sensitive to change over relatively short periods of time, correlated with clinical disability, but should also have a high pathological specificity. The recent EMA guidelines highlight that the reading of MRI images in clinical trials should be central and blinded [64].

4.2.1 MRI

Changes of whole brain atrophy represent the most used MRI outcome measure in trials of progressive multiple sclerosis, given the correlation with measures of disability [101], the excellent reproducibility and sensitivity to changes [66]. In healthy subjects, brain atrophy represents a physiological process and occurs at a rate of approximately 0.1–0.3 % per year; in SPMS this process happens faster, averaging about 0.5–1 % per year [66]. One important advantage of the methods used to calculate brain atrophy is that they are highly automated. They can be divided into 'registration-based' and 'segmentation-based' techniques. In the first group, structural image evaluation using normalization of atrophy (SIENA), brain boundary shift integral (BBSI), statistical parametric mapping (SPM), template-driven segmentation and voxel-based morphometry (VBM) are included [102]. Structural image evaluation using normalization of atrophy cross-sectional (x-sectional; SIENAX), brain parenchymal fraction (BPF), the brain to intracranial capacity ratio (BICCR), the Alfano method, Unified Segmentation (US) and k-Nearest Neighbour-based probabilistic segmentation (kNN) are in the second group [102, 103]. Atrophy measurement methods can also be improved by using 3D T1-weighted anatomical sequences [104]. One problem to consider when calculating atrophy in MS trials is the contribution of pseudoatrophy, defined as early transient (months) volume decrease due to an 'anti-oedema' effect of the drug under consideration (although this may be unknown at the outset).

Although MS is commonly considered a disease of white matter, grey matter (GM) involvement has been extensively described [105] and starts in the early stages of the disease [106–108]. The volume of GM tissue is lower in MS patients compared with healthy subjects [109] and quantification of GM atrophy represents a good potential outcome measure in clinical trials, given its correlation with long-term clinical disability [110, 111]. Also, pseudoatrophy is mostly confined to white matter rather than GM [112, 113]. VBM [114] and Freesurfer [115] represent common methods to calculate GM cortical atrophy in MS; however, lesion masks are needed in order to correctly classify lesions as white matter [25]. Semi-automated methods may improve the longitudinal analysis of GM atrophy [116, 117].

Black holes are an additional measure in SPMS trials. Demyelinating lesions appear hypointense on T1-weighted images during the active phase and it has been suggested that, after this phase of activity, the lesions that become isointense may show reduction of oedema and remyelination, whereas the lesions that remain hypointense after the phase of activity may be characterized by axonal loss [118, 119]. Persistently T1 hypointense lesions have been recommended as outcome measures for neuroprotection trials by an international workshop [66].

An important emerging outcome measure in MS clinical trials is spinal cord atrophy. Spinal cord atrophy is correlated with clinical disability and therefore has been proposed as a potential outcome measure in clinical trials of putative neuroprotective therapies [120, 121]. The development of a highly sensitive and reproducible method to quantify spinal cord atrophy has been challenging, therefore only a few clinical trials so far have used this measure as a neuroradiological endpoint [120, 122–124]. With recent technical improvements, the methods used to calculate spinal cord atrophy have changed from manual to semi-automated and fully automated methods. In 2010, Horsfield and colleagues described a method using an 'active surface model' that involved the placement of markers to automatically generate an outline of the spinal cord [125]. The best reproducibility in MS patients to date has been demonstrated by combining the MRI sequence three-dimensional phase-sensitive inversion recovery (PSIR) with the active surface model method [111].

The low pathological specificity of atrophy measures represents a major limitation, especially when testing putative neuroprotective agents. Proton MR spectroscopy (MRS) is able to detect and quantify different metabolites in the CNS, and has been widely studied in MS [126]. N-acetyl aspartate (synthesized in the neurons within the mitochondria), myoinositol (a glial metabolite), glutamate (a neurotransmitter inducing excitotoxicity), creatine (a marker of gliosis) and choline (a marker of membrane phospholipids, highly suggestive of ongoing inflammation when elevated) can be quantified with MRS and can improve the specificity for the pathological processes [127]. Although the longitudinal studies in SPMS patients and the application of MRS in SPMS clinical trials are still under review [66], guidelines for using MRS in multicentre clinical MS studies have been developed [128].

Finally, magnetization transfer ratio (MTR) is a technique that strongly reflects the amount of myelin in the brain [119], but can also be influenced by inflammation [129] and axonal density [130], whereas diffusion tensor imaging (DTI) can quantitatively detect brain microstructural changes by calculating parameters such as mean diffusivity, which is determined by the overall water motion and fractional anisotropy that reflects the uniformity of the direction of the diffusion of water molecules [131]. DTI measures may be considered as markers of demyelination and axonal loss [132].

Two key pathological processes in neurodegeneration are the alterations of mitochondrial function [43] and the redistribution of sodium channels in demyelinated axons [44]. These processes induce a modification of sodium content in the CNS that can be studied with a relatively recent MRI technique called sodium (^{23}Na) MRI [133]. Demyelinating lesions, normal-appearing white matter and grey matter in MS all have higher concentrations of sodium and there is correlation with clinical disability, supporting its application as a future possible outcome measure in SPMS trials [134–136].

4.2.2 OCT

Optical coherence tomography (OCT) represents a cheaper and quicker technique compared with MRI and has been proposed as a marker for neurodegeneration in MS [137]. It can measure the thickness of the retinal nerve fibre layer and the ganglion cell layer. Retinal axonal loss, regardless of clinical history of optic neuritis, may be a good marker of clinical disability in MS [135–139] and correlates with brain atrophy [140, 141].

4.3 CSF and Serum Biomarkers

At present, CSF and serum biomarkers have a relatively limited role as markers of neurodegeneration, mainly because of their high variability [142]. CSF heavy- and light-chain neurofilaments are stable proteins and correlate with axonal damage and clinical disability in MS [143–146]. Light-chain neurofilaments have already been used as outcome measures in clinical trials and await their final validation [25]. β-tubulin III is another cytoskeletal protein that can be used as a marker of neurodegeneration [147]. Serum biomarkers are clearly easier to collect than CSF, but have several limitations due to the influence of kidney and hepatic function and other ongoing infective or inflammatory diseases on their measured levels [148]. Their place at present awaits final evaluation and longitudinal study.

5 Trial Design

The classic 1:1 trials are time consuming and expensive, needing a high number of patients to be enrolled over reasonable durations to demonstrate efficacy. A number of alternative trial designs have been proposed in order to overcome this problem. Adaptive seamless trial designs combine phase II and phase III trials, and may

simultaneously test multiple drugs, using interim markers to define which treatments should be taken into phase III [149, 150]. For example, MRI outcomes could guide the interim decision, while clinical disability would be the phase III primary outcome. This strategy has the capacity to reduce both the duration and magnitude of SPMS trials compared with conventional designs [149].

Another approach is the 'Simon-2-stage studies' [151]. Here, in a first stage a small number of patients are enrolled and treated with the trial drug. If the drug shows an effect on the progression of the disability in a pre-determined number of patients, the study continues, otherwise it is stopped. The initial design is non-randomized, open label and single arm; however, advantages may accrue with reduced patients numbers and shorter trial duration, depending on the circumstances [150].

6 Conclusion

The lack of effective treatments for people with SPMS represents a major problem and the current evidence seems to support the hypothesis that neurodegeneration plays a major role, but is also part of a highly complex process. Here we have summarized the challenges related to the definition of SPMS, the pathophysiology of the disease and the outcome measures used in clinical trials. Attempts to clarify the pathogenesis of the disease and the mechanisms related to disability progression including the complex relationships between inflammation and neurodegeneration need to continue. The previous failures of classical immunosuppressants and disease-modifying treatments in SPMS have prompted the search for new drugs, not only targeting inflammation, but modulating neuronal protection. Two on-going phase II examples are SPRINT-MS (NCT01982942) in the US (ibudilast) and MS-SMART (NCT01910259) in the UK, a multi-arm trial (amiloride or riluzole or fluoxetine). Ideally, by improving the current imaging and laboratory measures, we will gain more specificity in the diagnosis, we will enrich our cohorts and this ultimately will translate into successful progressive MS therapeutics over the next decade. This was recently underlined by the exciting announcement of the positive ORATORIO (NCT01194570) trial of ocrelizumab in PPMS [152], which demonstrated a positive effect on progression of clinical disability sustained for at least 12 weeks.

Acknowledgements JC acknowledges the UK National Institute for Health Research (NIHR) University College London Hospitals/University College London Biomedical Research Centres Funding scheme.

Compliance with Ethical Standards

Funding There were no funding sources for the publication of this article.

Conflict of interest Jeremy Chataway is local principal investigator for trials in multiple sclerosis funded by Novartis, Biogen and GSK (agents not part of this review); investigator grant from Novartis outside this work; chief investigator of the EME funded MS-SMART trial [NCT01910259]. Domenico Plantone, Floriana De Angelis and Anisha Doshi are investigators of the EME funded MS-SMART trial [NCT01910259].

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