Secondary progressive multiple sclerosis — from neuropathology to definition and effective treatment

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ABSTRACT

Introduction. There is no single, commonly accepted, standard definition of secondary progressive multiple sclerosis (SPMS), an absence that poses a challenge for clinicians.

State of the art. SPMS is characterised by inflammation, neurodegeneration and disease progression with the presence or absence of relapses. No biochemical or radiological biomarkers are currently available to indicate the precise secondary progressive course in individual patients. The retrospective approach to identifying SPMS patients raises many difficulties, especially in terms of determining the time point of progression. Currently, the most precise diagnosis of SPMS is based on the definition proposed by Lorscheider et al., where SPMS is defined as a disability progression by 1 step on the Expanded Disability Status Scale (EDSS) in patients with EDSS ≤ 5.5 or of 0.5 EDSS steps in patients with EDSS ≥ 6 in the absence of a relapse, a minimum EDSS score of 4 and pyramidal functional system (FS) score of 2, and confirmed progression over ≥ 3 months, including confirmation within the leading FS.

Clinical implications. The need to establish criteria for the diagnosis of SPMS is currently of crucial importance due to emerging treatment opportunities including siponimod, a sphingosine 1-phosphate (S1P) receptor modulator selective for S1P1 and S1P5 receptors. It is reasonable to introduce drugs at the earliest possible stage of lesion progression to reduce inflammation and to protect the central nervous system (CNS) against irreversible neurodegeneration.

Future directions. Further studies with prospective, multicentre and long term follow-up design are needed to provide better insights into SP course in MS patients. This should be supported by radiological, biochemical and pathological evaluations to help establish reliable and sensitive biomarkers to guide clinical practice.

Key words: secondary progressive multiple sclerosis, disease progression, SPMS definition, SPMS neuropathology, SPMS treatment

Introduction

Today, secondary progressive multiple sclerosis (SPMS) is under extensive analysis. It is characterised by inflammation, neurodegeneration and disease progression with the presence or absence of relapses. Compared to patients with relapsing remitting multiple sclerosis (RRMS), patients with SPMS are usually older, have a higher degree of disability, a lower number of Gd+ lesions on T1-weighted images, and a larger volume of lesions on T2-weighted images on MRI [1].

However, the standardised definition of SPMS is yet to be established. There are currently no clear imaging, immunological, clinical or pathological criteria to determine the point at which RRMS converts to SPMS [2].

Establishing a uniform definition of SPMS would improve the comparability of clinical trials and observational studies...
and could offer better treatment results (faster patient enrollment for modern treatment modalities).

SPMS is difficult to diagnose retrospectively [2]. It is currently diagnosed based on a gradual worsening of the patient’s condition after the initial relapsing course with or without acute exacerbations during the disease progression. Conversion from RRMS to SPMS is observed 20 years after the diagnosis in 30–60% of cases (Fig. 1) [3].

It is necessary to carefully study the pathological mechanisms of disease progression to better understand the diagnostic and therapeutic targets in SPMS. Primary demyelination with partial axonal survival is the most characteristic process of RRMS, whereas brain atrophy is the main source of irreversible disability in progressive forms of multiple sclerosis (MS) [4]. Axonal degeneration begins early in active MS [5, 6]. However, initially, this does not result in disability. This is due to the fact that the human brain has an amazing ability to compensate [7]. Degeneration of demyelinated axons has been postulated as the leading feature of SPMS and a major cause of disability [4].

It seems that neuropathology could contribute to understanding the pathomechanism of SPMS. ‘Smouldering’ plaques within the white matter containing iron deposits are typical of SPMS, but these plaques are not found in RRMS. Importantly, iron plays a role in generating oxidative stress and neurodegeneration in MS [8]. These changes pose major diagnostic and therapeutic challenges and require further careful analysis.

Ruano et al. found that progressive forms of MS predispose to the development of cognitive disorders [9, 10]. Furthermore, it seemed that the thickness of cortical areas assessed in SPMS may be important in the impairment of attention in SPMS patients [11]. Assessment of both cognitive functions and fatigue has a great impact on the quality of life [12]. Kizlaatine et al. proved in their study that a composite marker of cognitive dysfunction with brain atrophy is a good differentiator between RRMS and SPMS [13]. Carotenuto et al. conducted an interesting study based on the relationship between cognitive impairment and olfactory impairment [14]. Patients with SPMS have more severe olfactory disorders, language and visuospatial deficits than do patients with RRMS [14, 15].

This information should be considered when searching for new drugs. Cognitive processes in SPMS patients may be impaired with disease duration and age. New drugs should have a significantly positive effect on improving daily functioning of patients. Siponimod is the latest recommended active SPMS treatment [16].

**Correlation between neuroimaging and MS progression**

Based on MRI findings, damage may be greater than predicted. Furthermore, disease progression is related to the failure of remyelination [17]. Focal plaques in the initial course of RRMS are only part of the processes, whereas lesions accumulate and become significant with disease progression [4]. Other neuropathological changes include spinal cord lesions, meningitis, grey matter lesions and diffuse damage to the normal-appearing white matter (NAWM) [18, 19]. Additionally, cortical demyelination [18, 19] and diffuse pathology (axonal injury, microglial activation, atrophy) were found in normal-appearing grey and white matter. However, they were not detected during standard follow-up tests [20]. Therefore, new methods to confirm disease progression in imaging studies should be sought to visualise the lesions that are not detected on standard MRI.

Grey matter atrophy could be a marker of disease progression. Furthermore, it could correlate with the degree of neurodegeneration [21]. Cerebral cortex thickness has been shown to correlate better with the degree of disability, including cognitive decline, compared to focal white matter lesions [22].

Degeneration of demyelinated neurons results in irreversible disability. The process is typical of SPMS [4, 23–25]. Therefore, grey matter atrophy may become a potential marker of SPMS. Various semi-automated longitudinal methods for measuring grey matter atrophy have been developed. They could be used in everyday practice in the future [26, 27]. Moreover, total brain atrophy and spinal cord atrophy also correlate with axonal loss and may be a sensitive biomarker of disease progression [6, 21, 28–30].

The retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) could be evaluated by optical coherence tomography (OCT). GCL correlates with the Expanded Disability Status Scale (EDSS). However, the RNFL is also correlated with brain atrophy and overall disability [31–33]. Thinning of the RNFL has been observed during SPMS despite the absence of relapses, and could represent the degree of brain neurodegeneration [34]. New imaging methods (e.g., diffusion tensor imaging and magnetisation transfer ratio MRI) could be used in future to assess disease progression [21].

**Neuropathology — the key to understanding SPMS**

MS is a chronic autoimmune disease of the central nervous system (CNS). According to the generally accepted theory, predominantly white matter myelin is the primary target of the
autoimmune attack. It is assumed that the processes of neurodegeneration are a secondary phenomenon. Nevertheless, they occur very early, and are closely related to inflammation [35, 36].

**Inflammatory component**

**T lymphocytes**

T lymphocytes are mainly represented by a subpopulation of CD3⁺, CD8⁺ cells and CD4⁺ helper cells. CD8⁺ cells are cytotoxic (granzyme B expression) or have the features of memory lymphocytes. The importance of CD4⁺ cells increased after the discovery of the Th17 subtype derived from the population of CD4⁺ lymphocytes mediated by transforming growth factor beta (TGF-b) and interleukin 6 (IL-6) [37]. Th17 lymphocyte activity is thought to be particularly high in the early stages of the immune attack (active plaque formation). These cells contribute to an increase in the permeability of the blood-brain barrier (BBB) [38]. CD4⁺ lymphocytes are responsible for the recruitment of macrophages, i.e. antigen-presenting cells, and thus participate in the formation of new demyelination. CD8⁺ lymphocytes tend to be in close contact with oligodendroglial cells and axons [39].

The above cells accumulate around the vessels, especially in demyelinating foci (plaques), forming dense infiltrates. They also infiltrate the pia mater, although their percentage there is lower than that of B lymphocytes.

**B lymphocytes**

B lymphocytes and the resulting plasma cells occur in the CNS during the RRMS much less frequently than T lymphocytes. A special role is assigned to CD20 and CD19. As in the case of T cells, they are also part of perivascular infiltrates. However, they are mostly present in the pia mater, forming structures with features resembling tertiary lymphoid structures with germinal centres [40]. The structures are mainly formed by large B-cells [41].

Thus, a vicious circle is formed in a particularly acute period of inflammation. Plasma cells produce immunoglobulins, especially IgG1 and IgG3 isotypes, and less frequently IgA and IgM. Oligoclonal IgA bands in the cerebrospinal fluid (CSF) are a marker of humoral immunity, whereas the presence of IgM is reported in a more aggressive course directed against myelin lipids [42]. B lymphocytes promote inflammation by direct and indirect effects on T cells. They secrete more tumour necrosis factor alpha (TNF-α) in the presence of pro-inflammatory interferon gamma (IFN-γ) produced by T lymphocytes. The destructive characteristics of B lymphocytes also results from overexpression of nitric oxide and hyper-reactive oxygen by these cells. Some authors have reported the ‘two-faced’ character of B lymphocytes in the pathogenesis of MS. On the one hand, these cells have a proinflammatory effect. On the other hand, they have an immunomodulatory effect by contact with T lymphocytes which secrete inhibitory cytokines, i.e. IL-10, TGF-β [43].

**Microglia/macrophages**

Long-term studies on the participation of microglia/macrophages in the pathogenesis of MS have confirmed the proinflammatory roles of these cells. They occur already in the early stages of the disease, initially particularly in active plaques in white and grey matter, especially in subpial plaques. Proliferation of microglia/macrophages also occurs in SPMS, not only in plaques but also in distant locations including NAWM. Their proinflammatory activity increases with the duration of the disease. These cells cause damage to the nervous tissue by antigen presentation via the major histocompatibility complex (MHC), releasing reactive oxygen and nitrogen, secreting proinflammatory cytokines and participating in phagocytosis. Demyelination, axonal damage, and neuronal degeneration are associated with a marked microglial activity [42, 44, 45].

**Demyelination/remyelination**

Myelin is the primary target of an immune attack. Firstly, degradation of myelin oligodendrocyte glycoprotein (MOG) occurs within two days. MOG is characterised by a low molecular weight and is expressed on the outer surface of the myelin sheath. Degradation of proteins with a higher molecular weight, especially myelin basic protein (MBP), occurs within six days. Myelin-associated glycoprotein (MAG), which is a structural protein and a component of the oligodendrocyte membrane, is also the target of attack [46]. Additionally, oxidative stress results in direct damage to oligodendrocytes with the loss of MAG and apoptosis. The above reactions are triggered and mediated by macrophages and active microglia that are abundant in inflammatory foci [47].

**Blood-brain barrier**

Autoactive lymphocytes, which are primed in the periphery, infiltrate the CNS to trigger an autoimmune reaction, which shows the basic role of the BBB in the pathogenesis of MS [48].

Crossing the BBB occurs through the interactions between lymphocyte integrins and adhesion molecules on the surface of endothelial cells. In acute active plaques, the BBB damage is centrally located in the most active area, whereas in the case of chronic active plaques the BBB damage is related to the rim [49].

**Neurodegeneration**

Degenerative changes in the CNS tissue are an integral part of the pathogenic picture of MS. The theory of primary myelin damage with the secondary activation of the processes resulting in neurodegeneration is commonly accepted [23]. Changes in demyelinated axons are the key point in the initiation of neurodegeneration. Severe Wallerian degeneration is mostly related to acute plaques. Less commonly, it may be also detected in diffusely abnormal white matter (DAWM) or even in NAWM [50]. It is mainly responsible for the loss of the white matter, considering the fact that as much as 45% of white matter mass is composed of axons and also responsible
for the loss of neurons in the cortex, and thus contributing to its atrophy [51].

Neuropathological changes and their location

Brain white matter

**MS plaques**

a) Acute plaques are characterised by extensive infiltration of CD68+ cells (macrophages / microglia). If macrophages are laden with myelin degradation products, particularly myelin basic protein (MBP), MOG, or MAG, the demyelinating lesion is acute. Slightly older ‘post-demyelinating’ plaques with numerous macrophages laden with non-specific lipid products do not show the presence of MAG or MOG (MAG-, MOG-). Both stages last 4-8 months. T and B cells are localised perivascularly and diffusely throughout the lesion area.

b) Chronic active plaques (so-called ‘smouldering’, mixed active/inactive lesions). Lymphocytic and macrophage/microglial inflammatory infiltrates involve the rim at the lesion border and decrease in intensity centrally. These plaques are characterised by a hypocellular lesion centre. Demyelination is pronounced in the centre of the plaques. The stages of early demyelination and post-demyelination are found on the rim with the occurrence of remyelination. Axonal damage is more extensive than in acute plaques and hypertrophic astrocytes are also detected.

c) Chronic inactive (‘burn-out’) plaques. These lesions are sharply demarcated from the surroundings. Myelitis and myelin destruction decrease in intensity. However, only a small number of T cells and microglia/macrophages are still present within the lesion. In addition to demyelination, these lesions are almost completely depleted of oligodendroglia and oligodendroglial progenitor cells, which hinders or even prevents remyelination. Axonal damage is evident, and axonal density is significantly reduced. However, scattered axonal swelling may indicate some ongoing neurodegeneration. Intense astrogliosis (particularly fibrous) changes the plaque into a gliotic scar [52].

Diffusely abnormal white matter (DAWM)

This area surrounds the plaques and is characterised by poorly defined borders and T-cell and B-cell perivascular and interstitial inflammatory infiltrates. Additionally, diffuse myelin pallor and the local loss of myelin are typical features of DAWM. Axonal damage and thinning are observed. Microglial and astroglial proliferation is evident. DAWM shows a predilection for periventricular location.

Normal-appearing white matter (NAWM)

In addition to plaques and DAWM, macroscopic appearance of the white matter shows no abnormalities. However, changes are found microscopically, particularly under higher magnification. BBB is damaged, myelin pallor, axonal damage, and local myelin and axonal loss are observed. Small diffuse inflammatory infiltrates are also present. Active microglial and astroglial proliferation is evident.

Brain grey matter

Grey matter damage occurs in the early stage of the disease and is a direct effect of inflammation, particularly in the pia mater. Neuronal loss in Wallerian degeneration is also present. Neuronal loss results in a massive loss of synapses.

Spinal cord

**MS plaques**

Approximately 80-90% of patients with MS present with plaques in the spinal cord. Their nature and dynamics are similar to those located in the brain. Considering the spinal cord parameters, even single lesions are crucial in generating clinical symptoms. The number of plaques ranges from a few to many lesions. Most lesions reach more than 3 cm on axial images. They show a predilection for lateral and posterior columns compared to anterior columns. Considering the thickness of the spinal cord, no significant differences have been observed in terms of the occurrence of plaques at different heights of the spinal cord.

Lesions involve the grey matter in about 20% of cases, and the white matter in more than 30%. In 45% of cases, lesions involve both. It is still unknown why the plaques are sharply limited to the grey or white matter [53]. Active lesions are more prevalent in the acute phase of the disease, but also occur in the advanced stage of MS.

Neurodegeneration

Axonal loss is present and affects axons of any calibre throughout the length of the spinal cord [54]. The degree of axonal damage correlates with the degree of myelin damage, whereas axonal density correlates with the duration of the disease [55]. Extensive axonal lesions are seen in the DAWM of the spinal cord. The origin of axonal lesions in the spinal cord is probably complex and some of them develop in active plaques in the spinal cord. Axonal damage also occurs in the course of Wallerian degeneration as a result of the activity of plaques and DAWM lesions in the brain.

Relapsing-remitting vs. secondary progressive multiple sclerosis — neuropathological aspects

Neuropathological changes in the CNS in RRMS and SPMS are basically similar and overlap [23]. However, the prevalence and severity of changes evolve with the duration of the disease.
Inflammatory/proliferative activity

In RRMS, active inflammatory changes in the form of plaques are prevalent mostly in the white matter. Macrophages are laden with early myelin degradation products. In SPMS, the number of newly formed active plaques in the white matter is significantly lower. However, many acute plaques in RRMS are transformed into chronic active plaques whose percentage in SPMS steadily increases in relation to acute plaques [56]. Inflammatory activity, although significantly reduced, persists permanently. Macrophages with early myelin degradation products still occur at the rim of chronic active plaques. A significant microglial reaction and diffuse astroglial reaction are noted in the vicinity of the plaques in DAWM and even in NAWM. Small perivascular inflammatory infiltrates are found in many areas of NAWM. They are surrounded by a narrow rim of degraded myelin. Damage to the NAWM affects approximately 90% of cases.

Inflammatory infiltrates in the pia mater that resemble lymphoid follicles are more prevalent in SPMS compared to RRMS. Their severity increases with the duration of the disease, and reaches a peak in early SPMS. Such infiltrates increase the risk of a more aggressive course of the disease against the background of diffuse CNS damage.

Neurodegenerative activity

Diffuse neurodegeneration in the white and grey matter is typical of SPMS. Marked axonal damage, reduced presynaptic endings, and neuronal loss are found in the cortex. These phenomena are mainly associated with two mechanisms i.e. retrograde Wallerian degeneration involving the white matter, and inflammatory infiltrates in the pia mater. Extensive demyelination, profound axonal damage and loss, and above all profound microglial and astroglial proliferation are predominant in the white matter. Astroglial proliferation is responsible for the formation of a dense fibrous scar, especially in previously active areas. The severity of scarring in advanced stages of MS can be so extensive that remyelination is not possible. The loss of grey and white matter of the brain and spinal cord is irreversible.

The mechanisms of degeneration in SPMS are not fully understood. On the one hand, ongoing inflammation in SPMS is involved in degeneration. On the other hand, an increasing failure of remyelination in neural structures damaged during RRMS is also reported [23]. There is no doubt that degeneration itself can initiate a secondary autoimmune response within the CNS, mainly from the microglia whose proliferation in SPMS is very high even without morphological indicators of haematogenic inflammation [57]. Due to the severity and extent of neurodegenerative changes, the ‘vicious circle’ mechanism (inflammation-neurodegeneration-inflammation) is particularly likely in SPMS.

Blood-brain barrier

Compared to RRMS, some of the most significant changes in SPMS are related to the BBB. The permeability of the damaged BBB with inflammatory activity is primarily related to the rim of the lesions with an increase in the number of chronic active plaques. Studies of the activity of BBB permeability markers in SPMS suggest the resealing of the BBB. If this is the case, then ongoing inflammation in SPMS is at least partly compartmentalised behind an intact BBB, which hinders or even prevents the penetration of drugs into the CNS [25].

Objective vs subjective definitions of SPMS

The division into the basic MS phenotypes (RRMS, primary progressive MS, SPMS) has been used for several decades. Definitions for the diagnosis of RRMS and PPMS (primary progressive multiple sclerosis) have been extensively defined using the 2017 revision of the McDonald criteria [58]. Unfortunately, no uniform definition of SPMS has been established yet.

The challenges associated with establishing a definition of SPMS result from difficulties related to the following factors: determining the degree of disability progression using the EDSS, determining the minimum score on the EDSS, determining the minimum degree and selecting the functional subscale, deciding on the necessity for the presence or absence of relapses, confirming disability progression at different time intervals (3-, 6-, 12- and 24-month intervals), determining the minimum time from the diagnosis of RRMS (usually at least 24 months and mostly 36 months) and determining irreversibility of disease progression.

To date, more than 570 definitions of SPMS have been presented. However, none has been commonly accepted. The existing definitions of SPMS are obtained from clinical trials and two significant manuscripts. Activities aimed at establishing the definition are based on these [3, 30].

One of the main difficulties in defining SPMS is the lack of easily reproducible and sensitive-to-change outcome measures in a relatively short time. Moreover, these measures should reflect the pathology causing irreversible physical disability typical of disease progression i.e. axonal damage or loss. In practice, the common outcome measures for SPMS are clinical and imaging outcome measures. The objective vs subjective definitions of SPMS are set out in Table 1.

The lack of a systematic definition of SPMS means that the inclusion criteria are not homogeneous, which hinders the interpretation of clinical trials [2, 21, 59]. Lorscheder et al. attempted to form a uniform definition based on the EDSS, FS, and the time necessary to confirm the diagnosis. The choice of such a definition allowed the establishment of a diagnosis three years earlier compared to retrospective physician evaluation. However, this definition did not consider MRI examinations, which made it difficult to clearly assess the disease activity. However, Lorscheder et al. emphasised that they wanted the definition to be easy and accessible [30].

When SPMS is described, the following definitions can be used: a “progressive disease” defined as steadily increasing, objectively documented, neurological dysfunction; and
Table 1. Proposed diagnosis of SPMS

<table>
<thead>
<tr>
<th>Subjective definition</th>
<th>Objective definition</th>
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<tr>
<td>Worsening of baseline state between relapses</td>
<td>Suggested tools for diagnosing SPMS</td>
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<tr>
<td>Retrospective confirmation</td>
<td>EDSS</td>
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<tr>
<td>Lorscheider et al. proposed definition of SPMS as:</td>
<td>— SPMS patients who scored 3.0–6.5 on EDSS</td>
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<tr>
<td>— disability progression by 1 step on EDSS in patients</td>
<td>— Evidence of secondary progression over at least the previous 2 years</td>
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<tr>
<td>— patients with EDSS ≤ 5.5 or 0.5 EDSS steps in patients</td>
<td>— Confirmed disability progression</td>
</tr>
<tr>
<td>— EDSS ≥ 6</td>
<td>— an increase of 1.0 point on EDSS or an increase of 0.5 points if EDSS was 5.5 or more</td>
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<tr>
<td>— no relapses</td>
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<tr>
<td>— minimum EDSS score of 4</td>
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<tr>
<td>— pyramidal functional system (FS) score of 2</td>
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<tr>
<td>— confirmed progression over ≥ 3 months</td>
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<tr>
<td>— including confirmation within the leading FS</td>
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<tr>
<td>MRI</td>
<td>Less frequently used criteria in clinical trials</td>
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<tr>
<td>Grey matter atrophy</td>
<td>— SPMS patients who scored 4.5–7.0 on EDSS</td>
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<tr>
<td>Total brain atrophy</td>
<td>— Progression was defined as sufficient to change FS on EDSS or effect a meaningful functional change</td>
</tr>
<tr>
<td>Spinal cord atrophy (loss of cervical axons)</td>
<td>— No evidence of relapse within 3 months prior to enrollment</td>
</tr>
<tr>
<td>Biomarker of CSF and blood</td>
<td>— Progressively worsened over the past 3 or 6 months</td>
</tr>
<tr>
<td>— Light chains of neurofilaments</td>
<td>— Disease activity was assessed by the onset of relapse or imaging results</td>
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<tr>
<td>— Axonal tubulin and actin</td>
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<td>— Gial fibrillary acidic protein (GFAP)</td>
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<td>— S100B</td>
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<tr>
<td>New diagnostic method</td>
<td>Limitations and problems related to objective definition</td>
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<tr>
<td>— Diffusion tensor imaging (DTI)</td>
<td>— Most definitions did not include ARR or MRI changes in the diagnosis of SPMS</td>
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<tr>
<td>— Magnetisation transfer ratio (MTR)</td>
<td>— The exclusion of patients with more relapses after diagnosis may not have a significant effect on the diagnosis</td>
</tr>
<tr>
<td>— Retinal nerve fibre layer (RNFL) and ganglion cell layer</td>
<td>— The frequency of relapses and Gd+ lesions is lower than in RRMS</td>
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<tr>
<td>— OCT</td>
<td>— 30, 70–72</td>
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</table>

“confirmed progression” defined as increased neurological dysfunction over a certain period of time (e.g. 3, 6 or 12 months) [2]. Clinical progression is not uniform, but may plateau and be characterised by periods of relative stability. The precise moment of transition from RRMS to SPMS is difficult in practice. Usually, the diagnosis of SPMS is made by neurologists retrospectively after several years of documented continuous neurological worsening.

An objective definition based on the EDSS and the FS would be useful in predicting the course of the disease. It seems to be particularly helpful in the systematisation of clinical trials. However, this definition does not include MRI imaging. Importantly, radiological progression in SPMS has not been clearly established [60]. It is known that Gd+ lesions occur less frequently. However, an increase in the number and volume of T1 lesions, a decrease in the brain volume, and changes in diffusion tensor imaging and magnetic transfer imaging, are more common [60].

It has been established that a minimum degree of disability is required to diagnose SPMS, whereas RRMS and SPMS are a continuum because relapses can occur in both forms [2, 29, 30, 61]. However, the annual relapse rate (ARR) during SPMS has been shown to be insignificant (0.23–0.26) [21]. Moreover, most definitions do not include ARR in the diagnosis of SPMS [21, 30].

Lorscheider et al. proposed a definition that most experts currently consider the most appropriate for the diagnosis of SPMS. This is as follows: disability progression by 1 EDSS step in patients with EDSS ≤ 5.5 or by 0.5 EDSS steps in patients with EDSS ≥ 6 in the absence of a relapse, a minimum EDSS...
score of 4 and pyramidal FS score of 2, and confirmed progression over ≥ 3 months, including confirmation within the leading FS. The accuracy of this diagnosis is 87%, as confirmed by three independent raters. Furthermore, it should be confirmed in the same FS to minimise the period of uncertainty (about two years) from the first symptoms to the final diagnosis [30].

In our opinion, the definition proposed by Lorscheider et al. most closely matches the assessment of SPMS. To confirm disease progression, it is important to obtain a minimal EDSS score and pyramidal FS score. The use of FS allows improvement in the internal validity of EDSS scores. The assessment of relapses after the diagnosis of SPMS does not affect the accuracy of the diagnosis [30]. However, we should be aware that the diagnosis of SPMS and its differentiation from other gradually progressive neurological disorders can remain elusive, being based mainly on clinical evaluation, without any fully reliable diagnostic tools e.g. MRI.

The question has also been posed as to whether SPMS occurs when progression between relapses is observed, or when the level of disability after another relapse is higher than after the previous relapse. Relapse-independent progression and relapse-related progression are both observed. However, as defined above, progression includes higher EDSS scores irrespective of relapse. The objective definition seems to be more sensitive than the diagnosis established by physicians (89% vs. 61%), which allows more frequent diagnosis of SPMS in future follow-up studies (18% vs. 9%) [4, 30]. It was found that in patients diagnosed with the use of the objective definition, a higher number of relapses was observed compared to those diagnosed by neurologists. This is probably due to the retrospective evaluation and the desire to administer disease-modifying drugs in the absence of other treatment perspectives [30].

The artificial division into RRMS or SPMS frequently causes problems during clinical trials. RRMS’s transition to SPMS is gradual. Indeed, the entire notion of ‘transition’ from RRMS to SPMS should be treated with extreme caution, because it suggests the existence of a transition zone known as the grey zone, which is a poorly defined term. Considering the criteria for immunomodulatory treatment, the patient is left in some sense without a diagnosis.

Therefore, it should rely particularly on the presence or absence of gradual progression and the presence of acute inflammation (i.e. active lesions and relapses) [62, 63]. Worsening of ambulation, cognition, gait balance, muscle strength, visual symptoms, bladder symptoms and fatigue have been reported by patients and clinicians to be related to the progression from RRMS to SPMS. Additionally, it should be borne in mind that disease progression can be accelerated by obesity, mental disorders, physical disability, and smoking [64]. However, no specific symptom definitively indicates progression to SPMS.

It may be useful to discuss the EDSS itself as a marker of progression. As previously mentioned, the higher the EDSS score, the lower the possibility of delay of disability progression [30]. Therefore, patients with a higher EDSS must be carefully monitored.

For example, post hoc analysis of the FREEDOMS trials showed that an EDSS-based definition may be more reliable than MRI lesion activity and relapses. SPMS was diagnosed when the EDSS score was assessed within six months in the absence of relapses or with relapses and when the initial EDSS ≥ 3.0 (increase by ≥ 1 for EDSS of 3–5 or by ≥ 0.5 for EDSS ≥ 5.5). The study revealed that EDSS scores were significantly predictive of conversion to SPMS, particularly the higher baseline EDSS > 3.5 [65]. Currently, the EDSS is the most widely used scale in MS clinical trials. It is an ordinal, nonlinear scale with high inter-rater variability and an overemphasis on walking ability. It should be noted that it can underestimate the scores related to cognition function, bladder dysfunction and upper extremity function, which is particularly crucial for the SPMS population.

The most important sign of SPMS is increasing motor dysfunction, independently of relapse-associated progression. The use of the EDSS to confirm the diagnosis of SPMS is consistent with the concept of a neurodegenerative length-dependent axonopathy as a central component of progressive MS [66, 67].

Basically, disability progression in the EDSS is expressed by an increase of 0.5 or 1 step over 3 or 6 months. As mentioned, at some level (mostly EDSS 6), patients persist for a long time despite overall disease progression. Therefore, the baseline EDSS score and progression over time seem important [62, 63].

All these limitations of the EDSS can be problematic. A definition based only on the clinical assessment (e.g. on the EDSS in the diagnosis of SPMS) could be insufficient. Research is ongoing to find biomarkers based on imaging and biochemical data (e.g. in blood or in CSF) that could be used for early identification of transformation in SPMS.

Progressive worsening of the baseline condition between relapses usually indicates transformation into SPMS [30]. Assessing this progression can be difficult due to the limitations of the EDSS. As already mentioned, the scale is mainly based on ambulation ability with EDSS scores > 4, and does not allow adequate assessment of upper limb function or cognitive function. The EDSS is characterised by variable results obtained by the same rater and by different raters [30].

Therefore, new diagnostic criteria are required. CSF markers are increasingly being mentioned in terms of facilitating the diagnosis. Light chains of neurofilaments (NfL) could be a potential indicator of disease progression, and their concentration correlates positively with the EDSS [68–70]. Higher serum NfL levels have been observed in patients with SPMS compared to patients with RRMS of the same age. Patients with high serum NfL concentrations are exposed to an increased risk of conversion compared to patients with low serum NfL concentrations (based on the FREEDOMS and TRANSFORMS studies). Other molecules that can be used as markers of astrocytic damage include axonal tubulin and actin, glial fibrillary acidic protein (GFAP), and S100B [71–73].
The disease may be stable over time [86, 87]. Experts have consensus as to how often MRI imaging should be performed. Should be assessed annually, regardless of relapse. There is no course of the disease. It is assumed that disease progression and a larger volume of lesions on T2-weighted images [80–85].

During follow-up visits, continuous assessment of patients for a gradual increase of symptoms not resulting from relapses (irreversible and persistent symptoms) seems to be the most important. Continued patient care by the same physician could be crucial. However, one study reported a 30% risk of overestimation of permanent disability assessed every 3–6 months [19], which could also pose a diagnostic challenge.

The use of an objective definition could reduce this problem. However, it can be difficult and complicated in everyday practice. There is a need to further explore the diagnostic problem related to SPMS.

Physicians should note the frequency of relapses. Leray et al. found that a high relapse rate within 2–5 years of a diagnosis of MS significantly increased the risk of conversion to SPMS and the risk of progression [74, 75]. Furthermore, relapses in chronic MS significantly increase disability progression [76]. Paz Soldán et al. presented clinical features affecting post-progression disability accumulation. Both pre- and post-progression relapses increase the rate of post-progression disability accumulation. Women accumulate disability slightly faster in the early stages of the progressive disease. Progressive MS occurs from the age of 50, and slightly increases the rate of post-progression disability accumulation [76].

On the other hand, the risk factors for the progressive form of the disease or shorter transformation time in SPMS include male sex and motor symptoms at the time of the disease [77–79]. As already mentioned, the duration of the disease is also important because within 20 years of diagnosis, conversion from RRMS to SPMS occurs in 30–60% of cases [77].

Compared to RRMS patients, subjects with the progressive form of the disease are usually older, have a higher degree of disability, a smaller number of Gd+ lesions on T1-weighted images, and a larger volume of lesions on T2-weighted images [80–85].

**Diagnosing SPMS in clinical practice**

Practical tools that will help predict the transition from RRMS to SPMS could be most beneficial to the everyday clinical practice of physicians. As already mentioned, the form of SPMS is mainly diagnosed retrospectively based on a gradual worsening of the patient's condition after a history of initial relapses with or without acute exacerbations during disease progression.

The objective definition can precede the diagnosis by many years. It seems that such a definition could contain both clinical and radiological data as well as laboratory test results [2].

**Diagnosing SPMS in clinical practice**

The primary goal of any proposed treatment for SPMS should be the prevention or delay of the accumulation of disability.

**Directions after diagnosis of SPMS**

After diagnosis of SPMS, it is necessary to assess the course of the disease. It is assumed that disease progression should be assessed annually, regardless of relapse. There is no consensus as to how often MRI imaging should be performed. The disease may be stable over time [86, 87]. Experts have demonstrated that the degree of recovery after relapse is not useful in determining the phenotype of the disease. However, residual disability contributes to the worsening of the disease over time [60].

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**Directions after diagnosis of SPMS**

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Disease activity expressed by relapse rates and new changes on MRI can be used to describe SPMS. Experts recommend the terms 'active' (in the case of Gd+ lesions on MRI or relapse) and 'progressive' (when clinical symptoms progress) [60]. As the data shows, inflammatory processes occur in all MS subtypes [88]. Treatment should start with the anti-inflammatory component. It is difficult to analyse SPMS in animal models. Therefore, the correct definition of SPMS could be useful in the proper conduct of clinical trials and in testing new drugs [4].

Treatment of SPMS is very problematic. This subtype is diagnosed late, CNS damage is advanced, and most drugs are ineffective. Furthermore, difficulty in determining the clinical benefits of the drug should be also stressed. It is very difficult to demonstrate such benefits, especially if the aim is not to prolong life but rather to postpone disability. The term 'time to wheelchair' is used to determine this aim. Some studies have revealed that the use of immunomodulatory therapy in the phenotype with relapses may delay the development of SPMS [76, 79]. However, research on this topic is not conclusive [76]. The treatment of SPMS still remains a significant problem to solve.

In the absence of alternative therapies, physicians could extend the treatment initiated in patients with RRMS symptoms who already have the SPMS phenotype. The accurate definition of SPMS would allow earlier diagnosis, faster testing of new drugs, and thus better treatment results. Establishing the right definition is crucial for further research into the treatment of SPMS.

As already mentioned, it is important whether the diagnosis is established by physicians or is based on criteria such as the EDSS. This can make a difference in diagnosis of as much as five years [62, 63]. Initially, the inflammatory processes can prevail despite the progressive form. In future, patients with a shorter duration of SPMS or early diagnosis will have different treatment perspectives compared to those with a longer course of the disease.

To date, the clinical results with dimethyl fumarate and natalizumab in patients with SPMS have not confirmed their effectiveness. Interferon beta has only been registered in Europe for the treatment of patients with active SPMS [8]. None of the drugs approved for RRMS has been shown to consistently decrease the progression of disability in SPMS as assessed by the EDSS.

In 2015, Ontaneda et al. showed in their study that nearly 20 compounds had been included in clinical trials within a period of five years [21]. Other substances that have been tested in the treatment of SPMS are discussed below.
The issue of vitamin D levels in MS patients is of crucial importance and may be significant in the treatment of SPMS. Research shows that high levels of this vitamin may have protective effects on myelin in normal-appearing grey and white matter [89]. Interestingly, another study showed a single case of SPMS regression following a ketogenic diet [90].

The MS-STAT randomised, placebo-controlled trial revealed that high-dose simeprevir reduced total brain atrophy and improved the quality of life in patients with SPMS [91]. The inclusion criteria were as follows: age 18-65, EDSS 4.0-6.5, and a diagnosis of MS based on the McDonald criteria (2017) with evidence of secondary progression over at least the previous two years. None of the patients was treated with disease-modifying drugs. These criteria did not include accurate information on the diagnosis of SPMS. The authors suggested a minimum period of two years of confirmed progression [91].

The recent EXPAND study has revealed the effectiveness of siponimod, i.e. sphingosine 1-phosphate (S1P) receptor modulator selective for S1P1 and S1P5 receptors. This molecule has been shown to reduce the risk of disability progression in patients with SPMS [16]. Another study confirmed the effectiveness of siponimod in patients with SPMS (particularly those with the active form). Furthermore, siponimod has shown neuroprotective effects [92]. That study included patients with SPMS and documented disease progression over the past two years in the absence of relapses or regardless of relapses, no evidence of relapse within three months prior to enrollment, and a median EDSS score of 3.0 to 6.5 at the time of inclusion in the study. Patients aged over 61 were not included in the study. In terms of disease activity, the characteristic features of inflammatory activity in SPMS may be associated with a relapse or imaging results (i.e. Gd+ lesions on T1-weighted images or active [new or enlarged] lesions on T2-weighted images) [16].

Mitoxantrone (MTX) is one of the approved forms of treatment for SPMS. It is used for EDSS scores of 3 to 6 [93]. The effectiveness of MTX administration has been confirmed by long- and short-term follow-ups [93, 94].

The potential risk of serious adverse events after MTX treatment, such as cardiotoxicity and acute leukaemia related to treatment, is also significant. It develops its effect on the immune system by reducing the number of T lymphocytes, the activity of cytotoxic T lymphocytes, inhibiting humoral immunity and the secretion of Th1 cytokines. As a result, it has a strong immunosuppressive effect. Overall, MTX can be considered as a form of therapy for very active MS, especially in regions with limited access to new immunotherapy [95].

High doses of biotin, which has neuroprotective properties [96, 97], may be used in the future for the treatment of SPMS. A randomised, double-blind, placebo-controlled study revealed a decrease in progression as assessed by the EDSS and a high safety profile of this treatment [97]. Patients included in this study (aged 18–75) were diagnosed with PPMS or SPMS using the revised McDonald criteria with clinical evidence of spastic paraparesis. Patients with clinical or radiological evidence of inflammatory activity within the previous year were excluded. Eligible patients had a baseline EDSS of 4.5–7 with evidence of disease progression during the previous two years (an increase of ≥ 1 point if the EDSS was 4.5–5.5 or ≥ 0.5 points if the EDSS was 5.5–7) [97].

Other molecules that may be important in the treatment of SPMS include alpha-lipoic acid [98]. The inclusion criteria in this study were as follows: age 40–70, prior RRMS (2005 McDonald criteria), and current SPMS defined by MS disability progression in the absence of clinical relapse during the previous five years as determined by a physician. Progression was defined as sufficient to change the FS on the EDSS or to effect a meaningful functional change (e.g. stopped working due to cognitive decline). Participants were allowed to start, stop, or continue glatiramer acetate or β-interferon during the study [98].

It is worth noting that SPMS and PPMS have been analysed together in most studies, leading to some difficulties in interpreting study results. 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. The authors of various publications have used different eligibility criteria for clinical trials for patients with SPMS. The inclusion criteria for various studies are set out in Table 2.

The results of selected studies on the use of immunomodulatory therapy in patients with SPMS have also been presented [81, 99–105]. It can be difficult to establish the definition of SPMS based on the conducted research. Regardless of treatment effectiveness, most researchers include patients with SPMS and an EDSS of 3-6.5 [16, 81, 100, 103]. To confirm progression, different time intervals were used in the studies (i.e. 3, 6, 12, or 24 months). In positive studies with siponimod, mitoxantrone and interferon beta, the criterion of 12, 6 or 3 months was used, respectively [16, 93, 100]. However, in negative trials with interferon beta and natalizumab, the criterion of 3 or 24 months was used, respectively [81, 103]. The most commonly accepted time to confirm a deficit assessed by the EDSS is 3 or 6 months [60]. Most of the studies set out in Table 2 did not exclude patients with relapses. However, in the study with siponimod, the eligibility criteria included no evidence of relapse in the three months before inclusion in the study. Objective definitions assessing disease progression using minimal EDSS levels seem to be more stable [30, 106]. Typically, disability progression has been defined as an increase of 1 point in the EDSS or an increase of 0.5 points if the EDSS was 5.5 or more [93, 97, 100, 103]. Patients with SPMS can experience not only relapses but can also present with Gd + MRI lesions. However, the frequency of relapses and Gd + lesions is lower than in RRMS (29-70%) [30, 107–109]. In the presented research, only the study with siponimod assessed disease activity on MRI as part of the inclusion criteria. The main limitation of most studies was the non-linearity of the
Table 2. Examples of eligibility criteria for clinical trials for patients with SPMS and results of selected studies on use of immunomodulatory therapy in patients with SPMS

<table>
<thead>
<tr>
<th>Study</th>
<th>Proposed inclusion criteria</th>
<th>Immunomodulatory drugs tested in the treatment of SPMS</th>
<th>Result of primary endpoint</th>
</tr>
</thead>
</table>
| Chan, D., et al., 2017 (MS-STAT) | - Age 18–65  
- EDSS 4.0–6.5  
- Diagnosis of MS based on 2017 McDonald criteria  
- Evidence of secondary progression over at least the last 2 years | High-doses of simvastatin | Reduced total brain atrophy and improved quality of life in patients with SPMS |
| Kappos, L., et al., 2018 (EXPAND) | - Age 18–60  
- SPMS diagnosis  
- Documented disease progression during the previous 2 years in the absence of relapses, or regardless of relapses  
- No evidence of relapse within 3 months prior to enrollment  
- Median score of 3.0 to 6.5 on EDSS at time of entry into study  
- Disease activity assessed by the onset of relapse or imaging results (i.e. Gd+ lesions on T1-weighted images or active [new or enlarged] lesions on T2-weighed images) | Siponimod | Reduced risk of disability progression |
| Tourbah, A., et al., 2016 (MD 1003) | - Age 18–75  
- PPMS or SPMS patients who were diagnosed using revised McDonald criteria  
- Clinical evidence of spastic paraparesis  
- Patients with clinical or radiological evidence of inflammatory activity within the previous year were excluded from the study  
- EDSS 4.5–7  
- Evidence of disease progression during the previous 2 years (an increase of ≥ 1 point if EDSS was 4.5–5.5 or of ≥ 0.5 points if EDSS was 6–7) | High doses of biotin | Decrease in progression as assessed by EDSS, and high safety profile of this treatment |
| Spain, R., et al., 2017 | - Age 40–70, prior RRMS (2005 McDonald criteria)  
- Current SPMS defined by MS disability progression in the absence of clinical relapse during the previous 5 years as determined by a physician  
- Progression was defined as sufficient to change the FS on the EDSS or effect a meaningful functional change | Alpha-lipoic acid | 68% reduction in annualised percent change brain volume |
| Lancet, 1998 | - SPMS patients who scored 3.0-6.5 on the EDSS  
- Confirmed disability progression (increase of 1.0 point on the EDSS or of 0.5 points if the EDSS was 6.0 or 6.5 for at least 3 months) | IFNβ-1b | European study was positive  
North American study was negative |
| Neurology, 2001 (SPECTRIMS) | - SPMS patients  
- EDSS between 3.0 and 6.5  
- Progressively worsened over the past 6 months  
- Confirmed disability progression (an increase of 1.0 point on EDSS or of 0.5 points if EDSS was 5.5 or more for at least 3 months) | IFNβ-1a | SPECTRIMS study was negative  
Study conducted by Nordic SPMS Study Group gave a negative result |
| Kapoor, R., et al., 2018 (ASCEND) | - Age 18–58  
- SPMS for 2 years or more  
- Disability progression unrelated to relapse in the previous year  
- EDSS 3.0–6.5 | Natalizumab | ASCEND study was negative |
| Martinelli Boneschi, F., et al., 2013 (MITOX, MIMS) | - Adult patients with SPMS  
- Regardless of age, gender, disability and duration of disease  
- Disability progression defined as increase by at least 1 point if EDSS < 5.5 or at least 0.5 points if EDSS > 5.5  
- EDSS assessed in two different and subsequent neurological examinations separated by at least a 6-month interval free of relapses | Mitoxantrone | Mitoxantrone reduced the progression of disability at two-year follow-up |
EDSS as it focuses on motor and lower limb functions, which can reduce the detection of subtle disease symptoms [30, 110]. On the other hand, a more stringent definition should include not only the EDSS score but also the FS, although the authors of the recommendations considered the possibility of deterioration or improvement within a different FS score with the same EDSS score [2]. Most studies did not use FS as an inclusion criterion. It is possible that the use of FS may improve the accuracy of the SPMS definition in the future. A gradual increase in time from diagnosis of MS to conversion to SPMS has been observed [111–116]. This may be associated with the MS phenotype, new drugs, or the heterogeneity of observational studies [22]. In studies with interferons, the time to progression was three months; in the case of siponimod it was two years [16, 100, 103].

Summarising the oldest studies with interferons, the inclusion criteria were very similar regardless of treatment effectiveness [100, 103]. Studies with mitoxantrone gave generally positive results in short and long-term follow-ups [11, 94]. The inclusion criteria for the study were very similar to those in the study with interferons [100, 103]. The study with sipimod considered changes on MRI. Most of the analysed studies did not take into account changes in FS in their criteria. The criterion of the mean EDSS (3–6.5) at the time of entry into the study was very constant [16, 81, 100, 103].

The authors used the definition of Lorscheider et al. After analysing a large group of studies, there are many inaccuracies that will require further research. Many compounds are under investigation, and new possibilities should be revealed in the future. Therefore, it is important to establish clear diagnostic criteria for SPMS to facilitate further research [8].

It has been reported that SPMS onset could be related to the most appropriate therapy model in RRMS. The most recent study proved that among patients with RRMS, initial treatment with highly active drugs (i.e. fingolimod, alemtuzumab, or natalizumab) was associated with a lower risk of conversion to SPMS compared to initial treatment with glatiramer acetate or interferon beta [117]. On the other hand, the rate of disability progression after the onset of SPMS was not associated with early disease course or treatment decisions. Relapses during SPMS were associated with accelerated disability progression, and immunomodulatory therapy was associated with improvements in disability outcomes in these patients.

These results confirm that inflammatory disease activity remains a substantial yet modifiable component of SPMS [118].

Summary

Two mechanisms are closely related to the development of SPMS: immune-inflammatory and neurodegenerative. Clinically, a gradual transition from RRMS to a progressive form of MS is observed. The authors of this article often struggled with the problem of diagnosing SPMS.

To facilitate the work of other physicians, we have created an overview of the available data on the SPMS definition. In our opinion, it seems that combining patient observation and systematic visits with available SPMS definitions may be helpful.

Current knowledge has not provided us with official SPMS criteria, as opposed to RRMS and PPMS forms (where we have the 2017 McDonald criteria). It seems that a definition which does not include MRI or other biomarkers might not be sufficient. Establishing the criteria for the diagnosis of SPMS is very important due to current and future treatment possibilities.

It is reasonable to introduce drugs at the earliest possible stage of lesion progression to reduce inflammation and protect the CNS from irreversible neurodegeneration [36, 119]. The updated criteria should include various aspects of this form. It is possible that this will be based on modern technologies such as diffusion tensor imaging (DTI), magnetisation transfer ratio (MTR), RNFL, and a better understanding of the pathomechanism affecting the development of this phenotype of MS.

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References


77. Tremlett H, Devonshire V. Natural history of secondary-progressi


80. Kappos L, Fazekas F, the MS-STAT randomised, placebo-controlled trial. The Lancet Neuro-


86. Hawk CM, O’Connor P. Freedman MS, et al. OLYMPUS trial group. Ritu


93. Chan D, Binks S, Nicholas J, et al. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. The Lancet Neuro-


