Progression in multiple sclerosis – a long-term problem

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Purpose of review
Disability progression in multiple sclerosis (MS) is strongly linked to central nervous system (CNS)-specific pathological processes that occur throughout all disease stages, but that become clinically evident in later phases of the disease. We here discuss current views and concepts for targeting progressive MS.

Recent findings
Detailed clinical assessment of MS patients has identified an even closer entanglement of relapse-remitting and progressive disease, leading to novel concepts such as 'progression independent of relapse activity'. Evolving clinical concepts together with a focus on molecular (neurofilament light chain) and imaging (paramagnetic rim lesions) biomarkers might specifically identify patients at risk of developing progressive MS considerably earlier than before. A multitude of novel treatment approaches focus either on direct neuroaxonal protection or myelin regeneration or on beneficially modulating CNS-intrinsic or innate immune inflammation. Although some long-awaited trials have recently been unsuccessful, important lessons could still be drawn from novel trial designs providing frameworks for future clinical studies.

Summary
Targeting progressive disease biology and repairing established damage is the current central challenge in the field of MS. Especially, the compartmentalized adaptive and innate CNS inflammation is an attractive target for novel approaches, probably as a combinatory approach together with neuroprotective or myelin regenerating strategies.

Keywords
biomarkers, disability progression, disease-modifying therapies, multiple sclerosis, prognosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory-driven autoimmune disorder that induces acute and degenerative processes within the central nervous system (CNS) [1,2]. The prevention of disability progression is of central importance in managing MS throughout all stages of disease. Current disease-modifying therapies (DMTs) mostly target focal inflammatory processes; an early efficient suppression of clinical and radiological features of focal CNS inflammation has a proven impact on long-term prognosis [3,4]. However, even current disease-modifying treatments are not able to fully control disability progression and a substantial number of patients still enter a secondary progressive phase of the disease. Furthermore, although there are some treatments approved for progressive MS, their clinical effect is rather moderate and especially evident in patients with clinical and/or radiological signs of disease activity. The clinical picture of progressive MS is defined by a gradual increase of disability independent of relapses, which can occur with disease onset (primary progressive; PPMS) or following a relapsing disease course (secondary progressive; SPMS). The differentiation between PPMS and SPMS is clinically relevant, for example due to regulatory reasons as some drugs are tested and approved only for one of these conditions (e.g., ocrelizumab for PPMS and siponimod for SPMS). However, evidence from clinical [5] or histopathological findings [6] rather underlines the similarities between both entities. Therefore, unless specifically

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KEY POINTS

- The prevention of disability progression is of central importance in managing multiple sclerosis (MS) throughout all stages of disease.
- Currently approved treatments for progressive MS have only modest clinical effects that are especially evident in patients with clinical and/or radiological signs of disease activity.
- Novel magnetic resonance imaging parameters such as paramagnetic rim lesions might allow selection of patients with ongoing chronic central nervous system (CNS) inflammation.
- Compartmentalized adaptive and innate CNS inflammation are attractive targets for novel therapeutic approaches, eventually in combination with direct neuroprotective and/or remyelinating strategies.

mentioned, we refer to PPMS and SPMS collectively as progressive MS (PMS) within this review.

CHALLENGES IN THE DETECTION OF PROGRESSIVE MULTIPLE SCLEROSIS

Why is it so difficult to understand, detect and treat disability progression in MS? PMS is a heterogeneic and multifaceted disease and animal models cannot properly reflect the complexity of disease biology [1]. Various interacting pathological processes leading to axonopathy and neuronal injury have been investigated; their interplay determines the rate of progressive tissue injury [7–9]. In parallel, genetic or environmental factors like smoking, obesity and vitamin D level contribute to CNS pathology.

In order to better define 'relapsing' and 'progressive' disease pathology, novel clinical subgroups of disease progression were defined that occur already in early phases of MS, including 'relapse-associated worsening' (RAW) and 'progression independent of relapse activity' (PIRA). Patients with a RAW MS type have frequent, severe relapses with a lack of recovery and the progression of disability proceeds very rapidly [3]. In patients with PIRA, however, progression of disability is independent of occurring relapses or MRI activity already in early phases of the disease [4]. Pathological studies have revealed chronically active (i.e., 'smoldering') lesions as one lesion subtype in MS patients that might be a correlate for continuous CNS inflammation that cannot be controlled by current therapeutic approaches [10]. Smoldering lesions are characterized by an inactive center and an active lesion edge consisting of interacting active glial and peripheral immune cells. Histological hallmarks are a disturbance of remyelinization, ongoing neuroaxonal loss and a slow continuous lesion growth (Fig. 1) [11▪▪,12]. Importantly, in MRI assessments, two independent approaches have been proposed as MRI correlates for chronically active lesions: Slowly expanding lesions (SEL) show a continuous and concentric enlargement in longitudinal routine T1/T2 sequences [13]. Furthermore, paramagnetic rim lesions (PRL) can be assessed in susceptibility-weighted sequences [14,15]. Expanding PRL are associated with a more aggressive disease course and worse outcome. MRI-informed histological assessment showed that PRL correlate with smoldering lesions as described above [11▪▪]. However, it is so far unclear whether SEL and PRL are correlates of identical pathological processes and how well they perform in clinical routine settings. As a next step, novel clinical trial designs focusing on patient subgroups defined by the presence of SEL and/or PRL indicative of ongoing CNS inflammation will be of great interest for the MS community.

So far, there is no gold standard in clinical routine to facilitate the diagnosis of progressive MS [16]. In clinical routine, the transition of RRMS to SPMS is often observed by patients and physicians with a significant delay since patients often do not notice the worsening of their disease. Therefore, treatment of progressive disease warrants both drugs reaching the CNS as well as those with protective or repair properties, and it warrants correct timing. The latter may be when progression can be detected or even already in the beginning of the disease since evidence is accumulating that progression may start prior to first symptoms. Current clinical parameters such as the Expanded Disability Status Scale (EDSS) or Multiple Sclerosis Functional Composite (MSFC) are not sensitive enough to detect early, subtle changes associated with progressive MS. Thorough examinations include, among others, a multimodal assessment of fatigue, anxiety, and cognitive deficits (e.g., Hospital Anxiety and Depression Scale (HADS), Symbol Digit Modalities Test (SDMT) or Brief International Cognitive Assessment for MS (BICAMS)) [17]. Cognitive impairment is associated with grey matter atrophy and brain network changes, and – while most frequently observed in patients with SPMS – can occur in all stages of MS. A randomized, placebo-controlled, crossover, double-blind trial recently investigated the efficacy of three potential drugs (amantadine, modafinil and methylphenidate) for treating fatigue in patients with MS [18▪▪]. Although none of these drugs had a significant effect on fatigue assessed by the modified fatigue impact scale, two encouraging lessons can be drawn: First, important deficits such as fatigue or

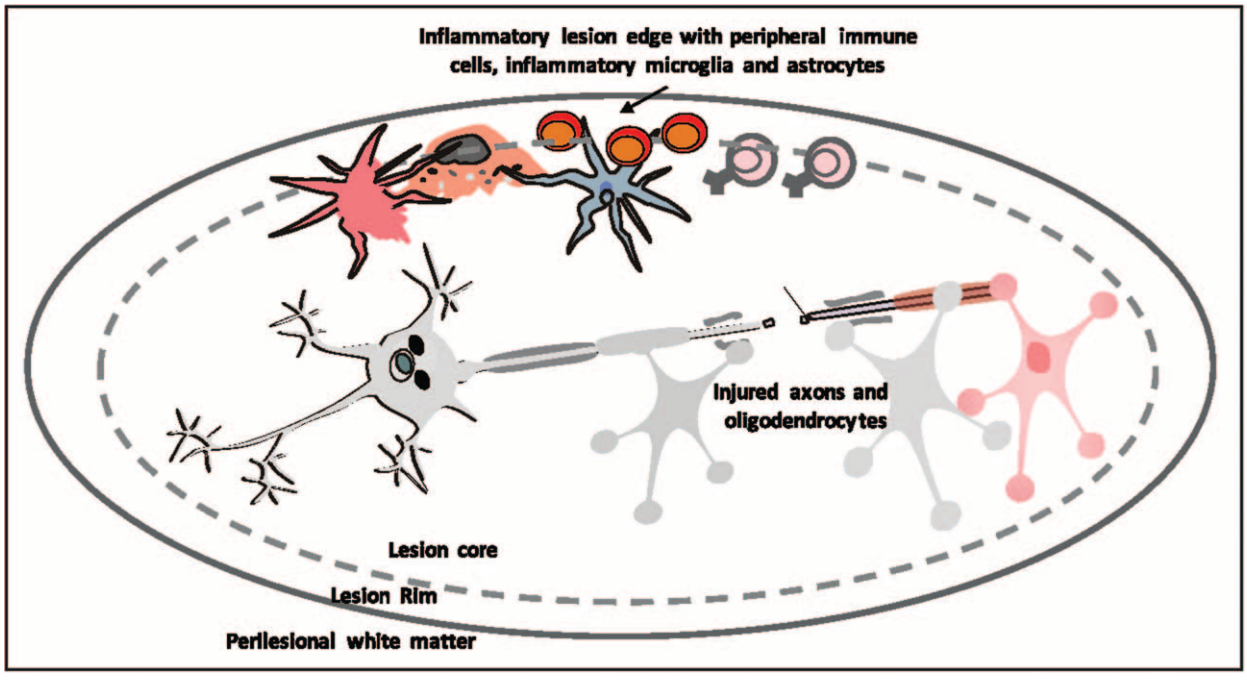

FIGURE 1. Smoldering lesions. According to Absinta *et al.* [11▪▪], glial cells interact with peripheral immune cells in chronic active lesion periplaque areas, resulting in ongoing microglia-/astrocyte-driven inflammation within the CNS. Within the lesion core, injured oligodendrocytes and a neuron are schematically outlined. CNS, central nervous system.

cognitive impairment are no longer only secondary endpoints in trials assessing relapse rate reduction or MRI parameters, but are finally moving into the center of assessing targeted treatment approaches. Second, the clinical trial design of four groups with different sequential drug changes allows the assessment of multiple potential drugs in one single trial thereby reducing the number of patients needed to participate. Surrogate markers specifically supporting the early identification of disease progression could greatly support clinical assessment. However, these are notoriously difficult to standardize and are mostly not yet part of clinical routine. Markers of neural degeneration including brain atrophy, quantitative spinal cord imaging, optical coherence tomography, and serum neurofilament light chains (sNfL) are the prioritized candidates for identifying progression [4,19▪].

TREATMENT APPROACHES IN PATIENTS WITH PROGRESSIVE MULTIPLE SCLEROSIS

With these facts in mind, there is an urgent need to develop drugs for PMS; however, treating PMS is still a huge challenge [7]. Although patients with RRMS benefit from 15 anti-inflammatory drugs that have regulatory approval, these therapies have no or only modest efficacy in PMS patients, since neurodegeneration and compartmentalized inflammation is difficult to target [1,7,20,21]. Natalizumab or sphingosine-1-phosphate receptor modulators are just a few examples of DMTs that reduce the impact of RRMS in patients but failed in trials for PMS [2]. However, DMTs like ocrelizumab (primary progressive) and siponimod (secondary progressive) gained market approval after successful results in clinical trials [2], although their long-term effect especially on patients with nonactive PMS is still unclear [1]. Especially in PMS, drugs that showed efficacy in clinical trials should be carefully observed in a real-word setting post market access, since treatment duration, population, co-morbidities, risk-assessment and especially higher age will differ outside of the clinical trial settings [22].

The development of suitable drugs for PMS from preclinical testing to clinical trials is proceeding slowly not least because discovering a new drug is a challenging, costly and time-consuming process [1,20]. Recently, despite promising results in smaller pilot trials, a phase III trial for biotin in patients with PMS assessing the proportion of patients with clinical improvement (i.e., decreased EDSS or improved 25-ft walk) yielded negative results [23▪]. Furthermore, primary endpoints could not be reached in the clinical trial program of laquinimod, which compromised both a phase III trial in patients with RRMS (primary endpoint: 3-month disability progression) and a phase II trial in patients with PPMS (primary endpoint: brain volume change after 48 weeks) [24▪,25]. Therefore, it can be helpful to

have a closer look at specific compounds of drugs for other neurodegenerative disorders (e.g., Alzheimer's disease) and test them in clinical trials regarding MS disease [1]. Using this process of drug repurposing, ibudilast and lipoic acid have been identified as successful in phase II clinical trials [1]. Also ibudilast (primary progressive) has recently demonstrated successful results in clinical trial phase II and is planned to be further tested in phase III ([26]; see also Table 1 for an overview of clinical trials for PMS).

In 2012, the International Progressive MS Alliance was founded to accelerate the development of effective treatment options for PMS [7,27]. They focus on identifying specific research areas to detect suitable targets for proper treatment and propose conducting experimental medicine trials to gather information about disease mechanisms within a short time frame [7,20]. Furthermore, they turned their attention to potential fluid biomarkers, particularly sNfL, which represents a marker of neurodegeneration [27]. sNfL levels might reflect neuroaxonal damage and could help identify treatment response and predict future disease activity [19▪]. As a body fluid biomarker, sNfL might be more pathologically specific and show a faster response towards treatment than imaging biomarkers like brain atrophy [27].

Ongoing clinical trials are addressing different aspects of PMS and might be roughly divided into three groups: first, it is highly attractive to prevent the worsening of disability with neuroprotective therapies targeting neuronal dysfunction and cell death. Preserving neuronal function is crucial, since the capacity of the brain to retrieve lost connectivity and repair damage is limited [21]. Recently, three promising substances that are already in clinical use for other indications were simultaneously tested in the MS-SMART trial: Amiloride blocks ASIC channels and reduces axonal calcium overload, riluzole targets glutamate-mediated excitotoxicity and fluoxetine provides trophic support for neurons by stimulating lactate release from astrocytes [28▪▪]. As none of these substances showed positive effects, it raises the question whether future trials should exclusively focus on axonal pathology, or whether other aspects of progressive inflammatory-mediated damage need to be targeted in combinatory treatment approaches. Nevertheless, simvastatin [29], ibudilast [26], lipoic acid [30] and masitinib [31]are additional promising neuroprotective substances that are currently tested in phase II and III clinical trials.

Second, promoting remyelination is another goal for successful treatment to regenerate and protect damaged axons in MS patients [21]. To observe remyelinating effects, current phase II clinical trials are testing, among others, bexarotene [32], opicinumab [33], erythropoietin [34] and clemastine fumarate [35] (see also [36] for an in-depth review on the topic). Importantly, most clinical trials assessing myelin regeneration focus on optic neuritis as a model system where demyelination and axonal degeneration can be assessed by visual evoked potentials and optical coherence tomography. No substance was so far able to show a benefit on overall clinical outcomes, whereas some positive data was obtained for magnetization transfer ratio (MTR), an imaging parameter indicative of remyelination [37,38].

Third, next to neuroprotective and remyelinating treatments, compounds targeting CNS-intrinsic inflammatory processes that are insufficiently controlled by peripheral immunomodulatory treatments are tested. The current most promising examples are substances targeting Bruton's tyrosine kinase (BTK) as a novel approach modulating both B cells and myeloid cells [39▪]. In B cells, BTK inhibitors block the maturation of B cells, thereby potentially targeting the generation of autoreactive B cells

Table 1. Selected clinical trials targeting progressive MS

Drug	Population	Mode of action	Status
Ocrelizumab	RMS and PPMS	B cell depletion	Approved
Siponimod	Active SPMS	sphingosine-1-phosphate receptor modulator	Approved
Evobrutinib, Tolebrutinib, Fenebrutinib	RMS and PPMS	Bruton's tyrosin kinase (BTK) inhibitor	Phase 3 ongoing
Masitinib	PPMS	Tyrosinkinase inhibitor in mast cells and microglia	Phase 3 completed
Simvastatin	SPMS	Unclear	Phase 3 ongoing
Lipoic acid	SPMS	Antioxidant intervention	Phase 2 completed
Ibudilast	PPMS and SPMS	Phosphodiesterase inhibitor	Phase 2 completed
Opicinumab	RMS	Promotes oligodendrocyte precursor cell differentiation	Phase 2 ongoing

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

while avoiding broad depletion of all B cells. Furthermore, BTK signaling is also involved in various myeloid cells (e.g., microglia and macrophages). However, this aspect of BTK blockade in MS patients is considerably less well understood as microglia also possess beneficial and reparative functions [40]. Various BTK inhibitors are under development; three are currently in phase III trials in MS patients (i.e., evobrutinib, tolebrutinib, fenebrutinib) [41,42▪]. Further strategies specifically modulating harmful aspects of microglia or astrocyte biology are to be expected in the future.

CONCLUSION

The development of successful treatment approaches for patients with PMS is a central challenge for the field of MS. In a multifaceted approach, progress is needed on several levels: From the development of animal models better reflecting progressive biology, to clinical tools and imaging/molecular biomarkers identifying patients at risk or in the first stages of progressive MS. Future treatment approaches focusing on CNS-intrinsic inflammation, neuroaxonal degeneration, and remyelination and repair strategies will hopefully not only substantially advance our understanding of progressive MS, but also lead to the approval of novel treatments.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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