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Pharmacotherapy in secondary progressive multiple sclerosis: an overview.

Floriana De Angelis[1], Domenico Plantone[1], Jeremy Chataway[1]

[1] Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, Faculty of Brain Sciences, UCL, London, UK.

Address:
QSMSC, UCL
10-12 Russell Square
London
WC1B 5EH

Corresponding author:
Floriana De Angelis,
Tel. 02031087419
Email: f.deangelis@ucl.ac.uk

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Abstract

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system characterised by demyelination, neuro-axonal loss, and a heterogeneous clinical course. MS presents with different phenotypes, most commonly a relapsing-remitting course (RRMS) and, less frequently, a progressive accumulation of disability from disease onset (primary progressive MS [PPMS]). The majority of people with RRMS, after a variable time, switch to a stage characterised by gradual neurological worsening known as secondary progressive MS (SPMS). We have a limited understanding of the mechanisms underlying MS, and it is believed that multiple genetic, environmental and endogenous factors are elements driving inflammation and ultimately neurodegeneration. Axonal loss and grey matter damage have been regarded as amongst the leading causes of irreversible neurological disability in the progressive stages. There are over a dozen disease-modifying therapies currently licenced for RRMS, but none of these has provided evidence of effectiveness in SPMS. Recently, there has been some early modest success with siponimod in SPMS and ocrelizumab in PPMS. Finding treatments to delay or prevent the courses of SPMS is an unmet and essential goal of the research in MS. In this review, we discuss new findings regarding drugs with immunomodulatory, neuroprotective or regenerative properties and possible treatment strategies for SPMS. We will look at the field broadly to include trials where participants have progressive or relapsing phenotypes. We will summarise the most relevant results from newer investigations from phase 2 and 3 randomised-controlled trials over the past decade, with particular attention to the last five years.

Key Points

- Many anti-inflammatory, reparative or neuroprotective agents are currently in the pipeline for secondary and primary progressive MS.
- New trial design may expedite the discovery of therapeutic compounds for progressive MS.
- The use of repurposed drugs and combination therapies are promising strategies to prevent or mitigate SPMS.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system (CNS) characterised by demyelination, neuro-axonal loss, and a heterogeneous clinical course. The most common presenting form of MS is relapsing–remitting (RRMS), affecting about 85% of the newly diagnosed patients. After 10-15 years, more than 50% of the RRMS patients convert to the secondary progressive stage of the disease (SPMS), characterised by slowly gradual neurological decline and none or rare relapses. In about 15% of the cases, MS has a progressive course since the beginning (primary progressive MS [PPMS]). The clinically isolated syndrome (CIS) is a condition characterised by one neurologic clinic event with associated neuroimaging features of demyelination that does not fulfil the MS diagnostic criteria.[1,2] The risk of conversion of CIS to clinically definite MS is about 45% within two years.[3] Finally, with the spreading use of MRI as a diagnostic tool, frequent incidental findings of diffuse white matter demyelination with a distribution similar to MS have been reported. Around two-thirds of these cases - called ‘radiologically isolated

syndromes' (RIS) - show radiological progression and one-third develop neurological symptoms during a mean follow-up of five years.[4]

We have a limited understanding of the mechanisms underlying MS, and a multidisciplinary approach is needed to clarify the complex pathophysiology of the disease. It is believed that many genetic, environmental and endogenous factors are important elements driving inflammation and ultimately neurodegeneration in MS.[5] Axonal loss and grey matter damage have been regarded as the leading causes of irreversible neurological disability in the progressive stages.[6–11]

During the past two decades, recent findings in the pathophysiology of MS have been translated into new therapeutics that mainly target the immune system centred on RRMS. Glatiramer acetate and betainterferons represent the first-generation disease-modifying therapies (DMTs) in MS, followed by a second-generation of DMTs initiated by natalizumab and fingolimod. Further agents such as teriflunomide, alemtuzumab, dimethyl fumarate, ocrelizumab and cladribine have been approved by the principal regulatory agencies – the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) - for RRMS (Figure 1). Despite their effectiveness in preventing new relapses or MRI lesions and in mitigating the disability progression in the short-term, less is known about their efficacy on disability in the long term. Furthermore, there is less evidence of a therapeutic effect of DMTs in progressive MS, and none of these can clearly stop the transition from RRMS to SPMS.

The purpose of this review is to discuss new findings regarding immunomodulatory, neuroprotective, remyelinating approaches and therefore potential future treatment

strategies for SPMS drawing broadly from the progressive and relapsing fields. We will look at recent data over the last five to ten years.

2. Pathogenesis of MS: from relapsing-remitting to secondary progressive phenotype

Many factors have been investigated in the pathophysiology of MS, although no specific trigger has been identified. Whether a CNS extrinsic or intrinsic factor drives MS is still not known. Viral infections (particularly by Epstein-Barr virus), vitamin D insufficiency, or smoking have been associated with a higher incidence of MS. The expression of the HLA alleles DRB1*1501, DRB1*0301, and DRB1*1303 on cells of the innate immune system are associated with an increased risk of developing MS (odds ratio [OR] 3.1, 1.26, and 2.4, respectively).[12] The commonly accepted hypothesis of MS pathogenesis is that multiple factors in combination (genetic, environmental and lifestyle) act in concert and trigger an immune-mediated inflammatory process. Macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system are the major contributors.[13] From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they activate microglia and macrophages. These induce the production of reactive oxygen species and nitric oxide, which in turn lead to neuronal mitochondrial dysfunction, energy failure and increased concentration of intracellular calcium and sodium. Acidosis and glutamate-mediated excitotoxicity contribute to increased intracellular concentrations of calcium and ultimately apoptosis of oligodendrocytes, and degeneration of axons and neuronal death.[14] B and T cells, monocytes, natural killer and dendritic cells are all involved in any stage of MS, explaining

why some therapeutics targeting inflammatory cells may be also effective in progressive MS.[15]

Despite the differences in clinical phenotypes, neuropathology studies have found that the patterns of inflammation are very similar between relapsing and progressive MS showing the same infiltrates - mostly CD8+ T lymphocytes, CD20+ B cells, and plasma cells – although the proportions of the single immune factors may differ. In RRMS, inflammatory infiltrates are associated with a blood–brain barrier (BBB) damage, and there is an abundance of new focal white matter lesions showing active demyelination. In progressive MS, instead, inflammation is compartmentalised behind an apparently normal BBB, and acute plaques are rare, while chronic plaques are abundant and show a slowly expanding rim of activated microglia and macrophages containing myelin degradation products at borders.[5,16] The concept that the BBB is intact in progressive MS, and therefore that mediators of DMTs cannot penetrate the CNS to exert their action, has been recently challenged by a study showing that there is a marked deposition of fibrin(ogen) – a marker of BBB disruption - in the cortex of progressive MS patients.[17]

MS plaque location is spread in the CNS of all phenotypes, involving both grey and white matter. In the later stages of the disease, there is diffuse and often extensive cortical demyelination that correlates with neuroaxonal loss, motor and cognitive disability.[18,19] Cortical demyelination extends along the subpial surface of the cortex and seems to be pathognomonic of MS, as there is no evidence of such a cortical damage in other neurological disorders. The exact pathogenesis of cortical lesions is debated, but it is believed to be linked to a local accumulation of pro-inflammatory cells or soluble factors from the meninges. In areas of reduced cerebrospinal fluid (CSF) flow, meningeal ectopic B

cell follicle-like structures have been identified and associated with SPMS, suggesting that meningeal inflammation may play a role in neurodegeneration.[20–22] Lisak and colleagues also demonstrated that B cells from patients with RRMS, but not from healthy controls, secrete factors *in vitro* toxic to neurons and oligodendrocytes independent of immunoglobulins, not complement-mediated, and involving apoptosis. They hypothesised that B cells entering the meninges and CSF from the peripheral immune system could secrete soluble factors different from antibodies that lead to the characteristic damage of MS in the underlying cortical grey matter.[23,24] Finally, profound diffuse pathology can be found in the normal-appearing white and grey matter, where there is evidence of perivenous inflammatory infiltrates surrounded by rims of demyelination, diffuse astrocytic gliosis, microglia activation and axonal degeneration.

From a diagnostic perspective, it may be difficult to identify the conversion from RRMS to SPMS or distinguish between PPMS and SPMS. To date, there are no clear pathologic, imaging, immunological or clinical criteria to identify the exact point of conversion from RRMS to SPMS, which is usually gradual and based on the observation of relentless increasing disability. Although PPMS and SPMS are considered as separate phenotypes, clinical, imaging and genetic data suggest that there are no pathophysiologically distinct features.[2]

3. Measures of neuroaxonal loss in MS clinical trials

A detailed description of clinical trial outcome measures is beyond the scope of this review and exhaustive reads of this topic can be found elsewhere. [25–28]

Clinical trials with 1–3-year follow-up in progressive MS have to infer long-term irreversible disability outcomes from short-term confirmed progression events. [29] Outcome measures related to progression vary across trials. The more recent phase 3 clinical trials primarily focus on the time to confirmed disability progression or the proportion of patients with or without confirmed disability progression. In phase 3 trials, disability progression is usually assessed on a clinical grounds by means of the Expanded Disability Status Scale (EDSS), the MS functional composite (MSFC) and its sub-components or recently by combination of EDSS and/or walking and/or upper limb progression . [30–32] Despite its widespread use, the EDSS is a nonlinear scale mostly weighted towards motor and lower limb functions and has shown low inter-rater and intra-rater reproducibility. [33] The MSFC is a composite score weighted on three components testing lower limb (timed 25-foot walk [T25FW] test), upper limb (9-hole peg test [9HPT], and cognitive functions (paced auditory serial addition test [PASAT]). The PASAT has been criticised due to its practise effects and patient frustration with the test. Like the PASAT, the symbol digit modalities test (SDMT) can measure speed of information processing, one of the cognitive domain more often affected in MS, most reliably and without causing anxiety in patients. The SDMT seems to be the neuropsychological test most sensitive to MS cognitive disorder and correlates well with MRI measures of atrophy and lesion burden, and it has been proposed that the SDMT should replace the PASAT in the MSFC. [34,35] In trials testing the visual pathways, and in general to add a sensitive measure of the vision function in MS trials, the Sloan low-contrast letter acuity have been used.[36,37]

In phase 2 trials, disease progression is measured by mean of imaging or laboratory biomarkers that have been linked to neuroaxonal loss.[38] Quantitative MRI can measure: 1) active Inflammation, by counting of new or enlarged T2 lesions or gadolinium-enhancing

lesions; 2) neuroaxonal loss, by calculating changes in whole brain volume (or regional grey matter and deep grey volumes) or spinal cord cross-sectional area, which are believed to reflect irreversible tissue damage, or atrophy. [39,40]

Studies of brain atrophy in clinically stable and untreated MS patients have shown that brain volume loss occurs at a rate of about 0.5–1% per year compared with 0.1–0.3% in healthy controls [41] and the brain volume loss is particularly pronounced in SPMS.[42–45] Neuroaxonal tissue constitutes a large proportion of brain volume and the increased rate of brain atrophy has been interpreted as evidence for neuroaxonal loss. [46] Moreover, brain atrophy significantly correlates with disability and cognitive impairment in MS.[47]

Advanced MRI techniques, such as magnetic transfer ratio (MTR) or magnetic resonance spectroscopy (MRS) may reflect specific myelin or neuroaxonal loss. [39]

The anterior visual system, which represents the most visible part of the human brain, is common site of damage in MS. Visual evoked potentials (VEPs) have been used for long time to objectively quantify the axonal integrity of the visual pathways and the VEP latency has been used to confirm the efficacy of remyelination or neuroprotective drugs. (Table 1-3). More recently, OCT has emerged in MS studies as a non-invasive tool that allows investigation of the neuronal retina. [48] OCT can quantify the thickness of the retinal nerve fibre layer (RNFL) made of unmyelinated axons originated from the retinal ganglion cell bodies. Ganglion cell layer and RNFL thicknesses are plausible biomarker of neuronal and axonal loss respectively. [49] In MS, some studies have reported significant associations between RNFL thickness and EDSS or MSFC, as well as with cognitive measures and brain atrophy. [50–54] A multicentre cohort study showed that decreased peripapillary RNFL thickness was associated with increased risk of disability worsening during follow-up in patients with MS. [55]

Laboratory biomarkers maybe useful to quantify the extent of neuroaxonal loss, with blood and CSF biomarkers such as osteopontin and neurofilament light chain levels starting to be measured in clinical trials.[56,57]

4. Agents under investigation: from relapsing-remitting to progressive MS

In order to modify the natural history of SPMS, preventing or delaying the accumulation of disability should be the goal of the treatment. T and B cells migrate from the peripheral blood into the CNS inducing local inflammation and producing immunoglobulins, which can be found in the CSF. The inflammatory activity of RRMS can be targeted in different ways, mostly blocking the trafficking of lymphocytes from the periphery to the CNS or by depleting the number of lymphocytes to reduce the amount of those that cross the BBB. In the progressive forms of MS, however, other cells, such as microglia and astrocytes, are believed to exert an important role and are now regarded as possible treatment targets.[58] New drug categories, such as putative neuroprotective agents, remyelination or neural repair agents are currently under investigation (Table 1-5).

3.1 Immune-modulation

Since the first DMT was released in 1993, many other immunomodulatory drugs have been tested in both RRMS and progressive MS. Clinical trials of betainterferons and glatiramer acetate in the progressive stages have given mixed results and overall have not shown clear

efficacy in preventing disability. In 2000, mitoxantrone, was approved for SPMS after the findings of the MIMS trial showing that the active arm experienced decreased relapse rate and disability progression. These effects were at least partially driven by the anti-inflammatory effect of mitoxantrone.[59] Nowadays, the use of mitoxantrone has been abandoned in many countries due to concern over safety.[60,61] However, short time course of mitoxantrone might be useful in very active MS as an induction treatment, with an acceptable safety profile.[62–64] The immunosuppressants azathioprine, cyclosporine, cyclophosphamide and methotrexate have been also trialled in both RRMS and progressive MS, leading to negative or inconclusive results. More details about these drugs have been extensively reported elsewhere.[25,65–67] We will describe here the agents that have been tested most recently in progressive MS, with a particular focus on SPMS (Table 1-3).

3.1.1 Negative trials

Alemtuzumab

Alemtuzumab is a chimeric monoclonal antibody targeting the CD52 surface protein mainly expressed by B and T lymphocytes.[68] An attempt of CD52-lymphocyte depletion with alemtuzumab has been tried in a small phase-2 trial with 36 SPMS subjects. [69] The study showed that patients relentlessly accrued clinical disability and MRI evidence of cerebral atrophy.[70,71]

Cladribine

Cladribine is a synthetic deoxyadenosine analogue chemotherapy agent that is activated by intracellular phosphorylation in specific cell types, such as lymphocytes. Cladribine-

phosphates interfere with deoxyribonucleic acid synthesis and repair in lymphocytes inducing their death and resulting in a targeted reduction of circulating lymphocytes.[72,73] Cladribine showed no efficacy on slowing disability progression and decreasing brain atrophy rates in a placebo-controlled trial in 159 patients with progressive MS, although some previous results from a small phase 2 trial had suggested positive effects. [74–76]

Dirucotide

Negative results were also obtained with dirucotide (MBP8298), a myelin basic protein (MBP) capable of inactivating autoreactive T and B cells and restore self-tolerance. Indeed, after a preliminary small trial showing that dirucotide significantly delayed clinical progression in patients expressing the allele HLA-DR2/DR4, two phase 3 trials - MAESTRO-01 and MAESTRO-03 - were commenced in patients with SPMS carrying the specific allele. In MAESTRO-1, dirucotide did not provide a clinical benefit compared to placebo and this led to the decision to early terminate the MAESTRO-03 trial. [77,78]

Fingolimod

Amongst the DMTs approved for RRMS, fingolimod (FTY720) is an antagonist of the sphingosine-1-phosphate (S1P) receptors that works by preventing lymphocytes egressing from lymphoid tissues into circulation and then migrating to the CNS. Fingolimod can cross the BBB and inhibits astrogliosis. In a clinical trial in RRMS, fingolimod significantly reduced brain volume loss. [79,80] Fingolimod has been investigated in the large phase 3 INFORMS trial in PPMS, showing that there was no difference in the rate of disability progression between the active and placebo arms.[81]

MIS416

MIS416 is a bacterial-derived microparticle capable of stimulating the innate immune system response. [82] Initially used for compassionate use in a few patients with SPMS in New Zealand, the drug was found to be safe and well tolerated in animal models of MS and in 19 patients with SPMS in a non-randomised phase 1b/2a open-label trial.[83] A further randomised, placebo-controlled phase 2b trial, however, did not show efficacy of MIS416 in the recruited 90 people with SPMS. [82,84]

Natalizumab

Natalizumab is a monoclonal antibody that targets the α4 subunit of the very late activation-4 (VLA-4) molecule on leukocytes, which blocks the transmigration of systemic immune cells to the CNS reducing inflammation. [85–87] In a small phase 2 open-label trial, natalizumab was associated with a decrease of osteopontin – a marker of neuronal damage - in progressive MS.[88] However, in the recently published phase 3 ASCEND trial, no treatment effect was observed on the primary outcome, a composite score combining EDSS, T25FW test and 9HPT used to measure the proportion of patients with confirmed disability progression over 96 weeks. Looking at the sub-components of the primary outcome, there was, however, a significant 44% reduction in the relative risk of confirmed upper-limb disability progression as measured by 9HPT (15% with natalizumab vs 23% with placebo; adjusted odds ratio [OR] 0.56 [95% CI 0.40–0.80]; p=0·001). [89]

Sulfasalazine

The anti-inflammatory and immune-modulator sulfasalazine, used as a DMT for rheumatoid arthritis, showed some efficacy in improving the outcomes of experimental allergic encephalomyelitis (EAE) and showed remyelination properties in animal models. However, it did not prevent the accumulation of clinical disability in active RRMS and progressive MS. [90,91]

3.1.2 Positive trials or promising results

Rituximab and Ocrelizumab

In 2008, the phase 2 HERMES trial showed that rituximab - a B-cell–depleting chimeric anti-CD20 monoclonal antibody – significantly reduced the number of gadolinium-enhancing lesions (GELs) and the number of relapses in RRMS when compared to placebo. [92] These findings changed the traditional view of the MS pathophysiology as an inflammatory disorder principally mediated by T cells. Rituximab was later on investigated in progressive MS, namely in the OLYMPUS [93] and RIVITaLISe [94] trial. Both these studies reported negative results. RIVITaLISe was terminated early, after an interim analysis showing a lower-than-expected depletion of intrathecal B cells that would have been insufficient to translate to potential clinical efficacy in a small phase 2 trial. In a subgroup of younger patients with active inflammatory lesions from OLYMPUS, selective B-cell depletion could reduce disease progression.

The findings from the OLYMPUS trial had a significant impact on further research and served as a rationale for testing ocrelizumab - another CD-20 monoclonal antibody - in both RRMS

and PPMS. The OPERA I and OPERA II phase 3 trials provided the evidence of ocrelizumab as a more effective drug over interferon-β in RRMS.[95] In the PPMS ORATORIO trial, patients on ocrelizumab showed lower rates of 12-week confirmed disability progression (primary outcome) versus placebo with a relative risk reduction of 24%. Eligibility criteria for ORATORIO included younger age (less than 55 years), evidence of CSF IgG oligoclonal bands, and disease duration no longer than 10 or 15 years according to EDSS. Ocrelizumab has received a licence from the FDA and EMA in PPMS.

Siponimod

Recent encouraging results have been reported from the phase 3 EXPAND trial that is investigating the efficacy of siponimod (BAF312) in more than 1651 patients with SPMS (siponimod n=1105 versus placebo n=546). Siponimod can cross the BBB, reduce CNS inflammation and promote mechanisms of repair via modulation of S1P1 on astrocytes and S1P5 on oligodendrocytes. [96,97] Results from the core study showed that siponimod reduced the risk of 3-month confirmed disability progression by 21% compared with placebo (hazard ratio [HR] 0.79, 95% CI 0.65–0.95; p=0.013). The increase in T2 lesion volume from baseline was significantly lower with siponimod than with placebo (between-group difference −695.3 mm^3, 95% CI −877.3 to −513.3; p<0.0001). Brain volume was preserved to a higher degree in the siponimod group than in the placebo group (mean percentage change over months 12 and 24 0.15%, 95% CI 0.07–0.23; p=0.0002). Siponimod did not reduce the time to 3-month confirmed worsening of the T25FWT, the key secondary outcome (HR 0.94, 95% CI 0.80–1.10; risk reduction 6%; p=0.44). [98][99]

Autologous haematopoietic stem cell transplantation

Autologous haematopoietic stem cell transplantation (AHSCT) induces an initial profound immunosuppression followed by a sub-sequent reconstitution of a qualitatively different immune system. This phenomenon might halt the progression of neurological disability and induce a prolonged medication-free interval. Muraro et al. reported the long-term results of a multicentre, observational, retrospective cohort study on AHSCT.[100] Progression-free survival in the subgroup with relapsing MS was 73% (95% CI, 57%-88%) at 5 years after AHSCT. Amongst patients with SPMS, the largest subgroup in the study, 33% (95% CI, 24%-42%) remained free from EDSS score deterioration with a rate of mortality of 2.8%. A recent meta-analysis has reported an increased risk of mortality in progressive patients with high EDSS scores that undergo AHSCT and a favourable effect in RRMS reaching levels of No Evidence of Disease Activity (NEDA) comparable with those reported from DMTs. This findings suggest that AHSCT may be a more effective alternative to approved DMTs in selected patients .[101] A phase 3 randomised trial is currently recruiting participants to assess the relative role of AHSCT versus alemtuzumab in adults with RRMS no older than 50 years of age, with EDSS ≤5.5 and the presence of significant inflammatory disease activity in the last year despite treatment with standard DMTs (NCT03477500).

3.1.3 Ongoing trials

Dimethyl fumarate

Dimethyl fumarate (DMF) may have a role in the treatment of progressive MS given its anti-inflammatory and neuroprotective properties.[102–104] Strassburger-Krogias and colleagues carried out an observational study in 26 patients with progressive MS (12 PPMS,

14 SPMS) treated with the fumarate mixture Fumaderm - approved for psoriasis in Germany - or DMF by pharmaceutical preparation.[105] They found no disease progression in more than 75% of the treated patients after a mean follow-up period of about 15 months. In 2015, the phase 3 randomised-controlled trial INSPIRE was started to further investigate the effects of DMF in SPMS. Due to the failure of the similarly designed ASCEND study, INSPIRE was terminated early. However, the phase 2 study FUMAPMS is currently recruiting participants to assess the efficacy of DMF in decreasing neurofilament light chain - a marker of neuronal damage - in 90 patients with PPMS after 48 weeks (NCT02959658).

Masitinib

Masitinib can inhibit mast cells activation. Migration and degranulation of mast cells in the CNS release proinflammatory and vasoactive mediators, which actively participate in the pathogenesis of MS.[106,107] Masitinib is being investigated in a phase 2/3 randomised-controlled trial assessing its safety and efficacy in lowering clinical disability in 450 people with PPMS and relapse-free SPMS (NCT01433497).[108] In a previous pilot phase 2 study in 12 PPMS and 18 relapse-free SPMS subjects, masitinib showed some therapeutic benefits on reducing the rate of upper and lower limb function impairment. [109]

3.2 Neuroprotection

Several mechanisms can be addressed to achieve neuroprotection. As reported by neuropathology studies, MS shows neuroaxonal loss at any stage of the disease, with a preponderance in the progressive courses.[6,110] A number of studies is currently investigating putative neuroprotective agents in progressive and relapsing MS (Table 2 and

4).

3.2.1 Negative trials

Dronabinol

Dronabinol is a cannabinoid that showed experimental evidence for neuroprotective effects.[111] Dronabinol was investigated in the placebo-controlled CAMS study looking for anti-spasticity effects. The CAMS study was negative, but it incidentally showed that patients with progressive course had alleviation of symptoms.[112] Dronabinol was then tested in the phase 3 CUPID trial, which did not show benefit on progression rate of dronabinol or in decreasing rates of brain volume loss. The unexpected low progression rate in the placebo arm may have affect the results.[113]

Erythropoietin

Erythropoietin can stimulate brain neuroprotection in experimental studies, promoting axonal repair, neurogenesis, and angiogenesis.[114] After a pilot study in chronic progressive MS, Schreiber and colleagues undertook a randomised, placebo-controlled, phase 2 trial of high-dose recombinant human erythropoietin in 52 progressive MS patients (34 had SPMS and 18 PPMS). They reported that erythropoietin did not improve the change in a composite measure of maximum gait distance, hand dexterity, and cognition from baseline to 24 weeks.[115,116]

Idebenone

Idebenone is a coenzyme Q10 analogue with antioxidant properties. Idebenone can decrease reactive oxygen species contributing to maintain a normal neuronal energy state.[117] A phase 1/2 adaptive study, the IPPoMS trial, had been recently reported showing no difference between the active treatment group and placebo in the rate of disability progression in the 77 randomised PPMS patients.[118] An open-label safety and efficacy extension of the IPPoMS trial was ongoing (NCT00950248 and NCT01854359). Full results are not available yet. [118]

Lamotrigine

Lamotrigine, licenced as an anticonvulsant, is thought to exert neuroprotective properties by blockade of sodium channels. In a phase 2 trial, lamotrigine failed in showing a reduction in brain atrophy rates over placebo in patients with SPMS. It was speculated that the results were affected by a high rate of nonadherence in the lamotrigine arm and by decreased brain volume during the first year of study likely due to pseudoatrophy. This is a phenomenon characterised by an apparent brain volume reduction, whose mechanisms can include fluid shifts or oedema resolution after the commencement of drugs with potent anti-inflammatory effects.[119,120]

Laquinimod

Laquinimod is another drug that has shown some neuroprotective properties in preclinical studies. [121] The phase 2 proof-of-concept ARPEGGIO trial, however, did not reduce MRI-

derived brain atrophy or the rate of confirmed disability progression over 48 weeks in PPMS (NCT02284568).[122,123]

Lithium

Lithium is a mood-stabilising drug that exerts anti-inflammatory effects and has shown some potential in reducing progression in animal models of several neurodegenerative diseases.[124] Rinker and colleagues reported the results from a 2-year, open-label crossover trial of adjunctive low-dose lithium carbonate versus standard care in 23 patients with progressive MS (3 PPMS and 20 SPMS). Subjects were randomly assigned to take lithium daily in year 1 or 2. Primary outcome measures were safety, tolerability and change in brain parenchymal fraction. Preliminary results showed a non-statistically significant decrease in brain atrophy over one year (brain parenchymal fraction increased by a mean of 0.560 ± 0.379%, compared to 0.139 ± 0.304% during standard care; p=0.399). Relapse rates and change in EDSS did not significantly differ between on- and off-lithium time periods. The authors concluded that low-dose lithium was well-tolerated and that preliminary analysis could not rule out a benefit on brain volume compared to standard care.[125] Full publication is pending.

Polyphenon E

Polyphenon E is a natural antioxidant agent capable to reduce oxidative stress in mitochondrial and consequent axonal injury. In 2011, the phase 2 POEMS study opened the recruitment to assess the safety and the neuroprotective effects of Polyphenon E in MS. Unexpectedly, Polyphenon E caused liver toxicity and the trial was terminated. [126]

3.2.2 Positive trials or promising results

Ibudilast

Ibudilast (MN166-001) has anti-inflammatory actions, and inhibits nitric oxide synthesis and tumour necrosis factor-alpha (TNFα), which is released by activated astrocytes and microglia. [127,128] In a phase 2 randomised placebo-controlled trial in RRMS, ibudilast was not effective in decreasing the number of relapses or new MRI lesions, but significantly reduced brain atrophy after 2 years. [129] Based on these results, the phase 2 SPRINT-MS study recruited 255 patients with progressive MS and tested the efficacy of ibudilast against placebo in reducing the rate of MRI-derived brain atrophy over 96 weeks. Preliminary results showed that treatment with ibudilast was associated with a 48% slowing in rate of brain atrophy (atrophy rate for ibudilast: -0.00105; 90% CI: -0.00160, -0.00049; atrophy rate for placebo: -0.00202; 90% CI: -0.00256, -0.00147). [130,131]

Lipoic acid

Lipoic acid is an antioxidant promoting free-radical scavenging, metallic ion chelation, regeneration of intracellular glutathione, and oxidative damage repair of macromolecules. It also takes part in the mitochondrial oxidative respiration and nucleic acid synthesis, and inhibits macrophage and microglial activation in EAE. [132,133] Spain and colleagues presented the results of a phase 2 study investigating lipoid acid in SPMS.[134] They showed that, after 2 years, participants taking lipoic acid had significantly less annualised percentage of brain volume change (−0.21% [SEE 0.14]) than controls (−0.65% [SEE 0.10], p = 0.002).

The beneficial effect size of lipoic acid treatment corresponded to a 0.44% ± 0.29% improvement in the rate of whole-brain atrophy (95% CI: 0.157-0.727).

Minocycline

Minocycline is a tetracycline antibiotic with immunomodulatory and neuroprotective properties capable of crossing the BBB, preventing microglial activation, glutamate excitotoxicity, and apoptosis. [135,136] Evidence supporting the neuroprotective role of minocycline has emerged from experimental models of acute neuronal injury (stroke, brain and spinal cord trauma), chronic neurodegenerative diseases (amyotrophic lateral sclerosis, Huntington's disease), and autoimmune CNS inflammation. [135,137] In RRMS, an open-label study of interferon-β and minocycline in 10 people with active RRMS showed positive effects on disease inflammation, decreasing the total number of GELs; whereas, no superiority was found in decreasing the number of GELs in the combination therapy of minocycline with glatiramer acetate or interferon-β 1-a versus injectable monotherapies in two double-blind, placebo-controlled phase 2 studies [138–140]. More recently, a study of minocycline versus placebo in 142 patients with CIS suggested that minocycline may delay the conversion to MS.[141]

The neuroprotective role of minocycline has not been investigated in progressive MS yet and whether this drug may have a role in the future trials in progressive MS is currently unknown.

Phenytoin

Phenytoin, similarly to oxcarbazepine, is a selective sodium-channel inhibitor with neuroprotective properties.[142] In a randomised phase 2 trial of 58 subjects with acute optic neuritis, the adjusted mean difference (i.e. phenytoin group minus placebo group) of retinal nerve fibre layer (RNFL) in the affected eye was 7.15 µm (95% CI 1.08-13.22; p=0.021) after 6 months. This result corresponded to a 30% reduction in the extent of RNFL loss with phenytoin compared with placebo, showing potential neuroprotection of the optic nerve.[143] Phenytoin has not yet been tested in progressive MS.

Simvastatin

Simvastatin is used for the treatment of primary hyperlipidaemia and secondary prevention of myocardial or cerebral ischaemia. Experimental evidence, however, suggested that statins can also exert anti-inflammatory and protective properties in the CNS. After some contradictory results from trials in RRMS, the phase 2 MS-STAT trial was undertaken investigating the effect of high-dose simvastatin versus placebo in reducing brain atrophy rate in 140 patients with SPMS over two years. They found that simvastatin significantly reduced the annualised MRI-derived brain atrophy rate by 43% (adjusted difference in atrophy rate between the groups: −0.254%; 95% CI: −0.422 to −0.087; p=0.003). [144] In the cognitive sub-study of the MS-STAT trial, there was evidence of a positive effect of simvastatin on frontal lobe function (difference 1.2 points, 95% CI 0.2 to 2.3 between baseline and month 24) and on the physical component of a quality-of-life measure (difference 2.5 points, 95% CI 0.3 to 4.8; p=0.028). [145] Following these positive results, the phase 3 study MS-STAT2 will shortly start the recruitment of 1180 patients with SPMS in the

UK. MS-STAT2 will assess the time to confirmed disability progression between simvastatin and placebo arm as measured by the EDSS after 36 months (NCT03387670).

3.2.3 Ongoing trials

Amiloride, Fluoxetine and Riluzole

The MS-SMART trial is a multiarm phase 2 placebo-controlled study investigating the putative neuroprotection properties of amiloride, fluoxetine and riluzole in 445 patients with SPMS.[146] Amiloride is an acid-sensing ion channel-1 (ASICS1) blocker. Recent studies have shown that ASIC1s contribute to axonal degeneration in CNS lesions. In MS, ASIC1s seem to activate under acidic conditions predominating in the inflammatory CNS lesions leading to a Na+ and Ca2+ overload and following damage and apoptosis of axons. [147] A pilot open-label study in 14 patients with PPMS, showed that amiloride significantly reduced the rate of MRI-derived brain atrophy.[148] The same research group and independently an Austrian team investigated the effect of amiloride in patients with acute optic neuritis. [149] The former study showed no neuroprotective benefits. Report of the results from the latter has not been presented yet (NCT01879527). Fluoxetine is a selective serotonin-reuptake inhibitor with pleiotropic neuroprotective effects stimulating glycogenolysis and improving mitochondrial energy metabolism.[150,151] Mostert and colleagues carried out a pilot 2-year randomised, placebo-controlled phase 2 trial in 42 people with progressive MS (29 SPM and 13 PPMS) and showed no evidence of a significant clinical benefit.[152] However, this study had a low sample size and the same research team carried out a further trial in progressive MS, using as primary outcome measure time to confirmed disease progression defined as either at least a 20% increase in the T25-FW or at least a 20% increase in the 9-

HPT. They reported a trend (p= 0.07) towards significant difference in time to confirmed disease progression between fluoxetine and placebo groups. MRI results are expected. It was speculated that the study was underpowered to detect a significant clinical effect over the 2 years of the trial.[153] Riluzole antagonises voltage-dependent sodium channels and is a glutamate receptor modulator that inhibits the synaptic release of glutamate, which is a neurotoxic agent. A pilot study of riluzole in PPMS showed a reduction of the rate of cervical cord atrophy and the number of new brain T1 hypointense lesions.[154] Waubant and colleagues, investigated the neuroprotective effect of riluzole versus placebo in early RRMS patients as an add-on to interferon-β 1a. They reported no difference between placebo and riluzole on brain atrophy as measured by MRI.[155]

Oxcarbazepine

Oxcarbazepine may have neuroprotective properties by blocking sodium channels. Oxcarbazepine is being investigated in the PROXIMUS study, a phase 2a trial that recruited patients in the early stage of SPMS who were still on DMTs. The rationale behind this study is the attempt to treat SPMS addressing both neurodegeneration with oxcarbazepine and inflammation with approved DMTs. Quantification of CSF neurofilament light chain is the primary outcome measure of the trial (NCT02104661).

3.3 Regenerative therapies

This therapeutic approach to MS is new and a number of agents are currently being investigated (Table 2 and 5)

3.3.1 Negative trials

GSK239512

GSK239512 is a selective and brain penetrant H3 receptor antagonist capable of promoting oligodendrocyte progenitor cell differentiation *in vitro* and enhances remyelination in the cuprizone mouse model of remyelination.[156] In a pilot placebo-controlled phase 2 study, GSK239512 had a good safety profile and a small positive effect on remyelination as measured by magnetisation transfer ratio (MTR) in a cohort of 131 RRMS patients, although there was no effect on clinical or conventional MRI parameters. It was speculated that the development of clinical endpoints more directly linked to changes in myelination or the inclusion of a population with more disease activity, or a longer trial duration would have been more appropriate to explore the impact of GSK239512 on the disease. [157]

Opicinumab

Not formally assessed in patients with progressive MS, the human monoclonal antibody *opicinumab* (BIIB033 or anti-LINGO-1) has shown remyelination and neuroprotective properties in animal models of MS.[158–161] In the phase 2 RENEW trial, 82 participants with acute optic neuritis were randomised to receive opicinumab or placebo. The primary endpoint was remyelination at 24 weeks, measured as recovery of affected optic nerve conduction latency using full-field visual evoked potential (FF-VEP) versus the unaffected fellow eye at baseline. Remyelination did not differ significantly between the opicinumab and placebo groups in the intention-to-treat population at week 24. However, results from the pre-specified per-protocol population at week 24 (14.7 vs 22.2 [−15.1 to 0.0]; 34%; p=0.050) suggested that opicinumab could enhance remyelination in the human CNS. [162]

SYNERGY was a phase 2 study investigating the additive efficacy of opicinumab to interferon-β 1a in patients with RRMS. Preliminary results showed that the trial did not meet the pre-specified primary endpoint. [163] The phase 2 AFFINITY trial is ongoing to evaluate the effects of opicinumab, as an add on therapy to anti-inflammatory DMTs, on disability improvement over 72 weeks in relapsing MS (NCT03222973).

3.3.2 Positive trials or promising results

Biotin

Biotin (MD1003) can increase energy production in demyelinated axons and enhance myelin synthesis in oligodendrocytes, behaving as both neuroprotective and myelin repair drug.[164] After an open-label pilot study of biotin in 23 progressive MS (both SPMS and PPMS) showed that patients had qualitative or quantitative improvement, Tourbah et al. reported the results of the MS-SPI trial. The primary endpoint was the proportion of patients with improvement of MS-related disability (measured with EDSS or timed 25-foot walk) at month 9, confirmed at month 12. They found an improvement of MS-related disability at month 9, confirmed at month 12, in 12.6% of the patients, and a reduced proportion of patients with EDSS at month 9 (confirmed at month 12). [165,166] Interestingly, an MRI sub-study of the trial showed an improvement in MTR and fractional anisotropy on diffuse tensor imaging (DTI), markers of myelin density and axonal integrity respectively, and a reduction of whole brain volume and grey matter volume. The decrease in brain volume was perhaps due to pseudoatrophy.[167] Further results from the placebo-controlled crossover MS-ON trial of biotin in patients with progressively worsening optic neuritis did not meet its primary outcome - a mean change in 100% contrast visual acuity at

6 months.[168] The confirmatory phase 3 SPI-2 trial is currently recruiting patients with progressive MS (NCT02936037).

Clemastine fumarate

Clemastine fumarate promotes oligodendrocyte precursor differentiation and remyelination without modulating the immune system. Green et al. reported the results from the crossover, randomised, placebo-controlled phase 2 ReBUILD trial, where clemastine fumarate was used in patients showing chronic optic neuritis and evidence of visual evoked potential (VEP) P100 latency of 118 ms and RNFL >70 µm. The primary outcome was a shortening of P100 latency delay on full-field, pattern-reversal VEPs. The primary pre-specified efficacy endpoint for the trial was met with reduction of latency delay of 1.7 ms/eye (95% CI 0.5–2.9; p=0.0048) in the crossover model.[169]. A new phase 2 trial on clemastine fumarate in acute optic neuritis is now recruiting aiming at assessing the degree of recovery with or without clemastine (ReCOVER trial, NCT02521311).[170]

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have multipotent mesodermal differentiation potential and can promote tissue repair through the release of paracrine factors. MSCs can also inhibit gliosis and promote oligodendrogenesis, showing neuroprotection properties. Intravenous administration of MSCs or their derivatives is protective against EAE in mice. [171,172] Pilot studies have supported the safety or the potential efficacy of MSCs.[173–176] An open-label phase 2a proof-of-concept study in 10 SPMS patients showed that disease improved on measures of visual function, visual evoked potentials, and imaging showed an increase in

optic nerve area.[177] A small randomised placebo-controlled phase 2 crossover study in 9 patients with RRMS suggested a trend to lower cumulative GELs at brain MRI.[178] A recent phase 1 open label trial of intrathecal autologous bone marrow MSC-derived neural progenitor showed good safety and tolerability and suggested possible clinical improvement in patients with progressive MS.[179]

3.3.3 Ongoing trials

ACTH

ACTH used to treat MS relapses acts via corticosteroid-independent melanocortin pathways suppressing CNS proinflammatory cytokines.[180] A randomised clinical trial of ACTH pulse therapy in progressive MS is currently recruiting participants. Safety, tolerability and efficacy of ACTH on walking test at 36 months will be assessed (NCT01950234). At the same time, a phase 4 trial is recruiting patients with RRMS or SPMS to determine if monthly pulse doses of a three-day course ACTH is more effective than one course at recovering myelin at 12 months, as measured by MRI myelin water fraction, in new multiple sclerosis lesions (NCT02446886).

Domperidone

Domperidone can increase the levels of prolactin, which seems to improve myelin repair in mice. A Canadian group is now leading an open label phase 2 futility trial assessing the efficacy of domperidone in 62 patients with SPMS. This study is currently recruiting participants (NCT02308137).[181]

Quetiapine fumarate

Quetiapine fumarate, an atypical antipsychotic, may have remyelination properties. [182] The University of Calgary, in collaboration with the Multiple Sclerosis Society of Canada, is now recruiting patients with RRMS and progressive MS in a phase 1/2 trial with the purpose to test the safety and dose tolerability of quetiapine (NCT02087631).

Triiodothyronine

A phase 1 study is addressing the safety and tolerability of high-dose thyroid hormone (triiodothyronine or T3) as a putative remyelinating drug for MS (NCT02760056). Indeed, T3 is thought to enhance remyelination in the adult brain by the induction of oligodendrocyte maturation. In cuprizone-induced demyelination mice, T3 promotes remyelination in chronic lesions by both enhancing oligodendrocyte maturation and attenuating astrogliosis.[183]

3.4 Other approaches

3.4.1 Antiviral therapies

GnbAC1

Human endogenous retroviruses (HERVs) are present in a latent form in the human genome, and in patients with MS. HERV-W - known as the MS-associated endogenous retrovirus — can be activated by environmental factors and produces a pathogenic surface envelope protein. This envelope protein can contribute to MS pathogenesis by inducing the activation of proinflammatory macrophages and inhibiting neuronal remyelination. GnbAC1

is a monoclonal antibody directed against this human retroviral protein that appeared to be safe in 33 healthy subjects and 10 MS patients. [184,185] Recently, GNbAC1 has been investigated in the randomised placebo-controlled phase 2 CHANGE-MS study in RRMS. The results showed no effect on inflammatory measures (including the number of GELs) over weeks 12-24. However, a post hoc analysis suggested that GnbAC1 18 mg/Kg may have remyelination properties according to the increase of MTR values in the cortical grey matter bands (band 3 ΔMTR between baseline to week 24 was 2.167% [percentage unit] change, p=0.059). Given the evidence of some remyelinating properties, the use of GnbAC1 may be considered for SPMS in the future. [186] Full publication of this study is pending.

3.4.2 Immunotherapy

ATX-MS-1467

Induction of antigen-specific immune tolerance, or immunisation, is now a feasible approach to autoimmune disorders. ATX-MS-1467 is made of four peptides of a myelin protein commonly attacked in MS. Once injected, the antigens carried by ATX-MS-1467 are taken up by immature antigen presenting cells, which instead of inactivating T cell or convert them to a T-cell type that maintains tolerance. [187] In animal models of MS and 6 SPMS patients, Streeter et al. have demonstrated that daily injection of ATX-MS-1467 was well-tolerated and led to inhibition of EAE and disease progression. [188] More recently, the results from two open label phase 1 and a phase 2a proof-of-concept studies showed that ATX-MS-1467 is safe, well-tolerated, and potentially effective in RRMS. Indeed, in the phase 2 study, there was a statistically significant decrease in the number of T1 GELs on treatment

compared with baseline (from 7.4 ± 7.62 to 5.0 ± 7.24; p = 0.0143) based on a nonparametric analysis.[189]

NeuroVax™

Vaccination with the T cell receptor (TCR) complementarity determining regions 2 (CDR2 peptide associated beta variable (BV) gene was able to cure EAE.[190] Development of TCR peptide vaccination for MS required identifying target TCR BV genes and creating a vaccine capable of reliably boosting TCR reactive T cells.[191,192] Gold et al. carried out a small study of vaccination with a TCR BV6S5 CDR2 peptide emulsified in incomplete Freund's adjuvant (IFA) in MS. They reported no clinical benefit in the immunised patients, but there was evidence of a decreased number of activated BV6S5 T cells within the CNS.[193] Since then, many other TCR BV targets have been used. For instance, in a phase 1/2 study, Bourdette and co-workers investigated the immunogenicity and safety of combined administration of CDR2 TCR peptides (BV5S2, BV6S5 and BV13S1) emulsified in IFA. They showed that the trivalent TCR peptide vaccine in IFA strongly boosted circulating frequencies of TCR-reactive T cells in 100% of MS patients (including SPMS and RRMS), whereas a low rate of successful vaccination (20%) was found within subjects treated with individual TCR peptides in saline. No statistically significant differences were found in MRI activity between the TCR responder and non-responder groups. However, this study was small, including 37 subjects, and short (24 weeks). A study of NeuroVax™, a therapeutic TCR peptide vaccine, is currently ongoing in SPMS (NCT02057159).

Tcelna

Tcelna (previously known as Tovaxin) is an autologous T-cell immunotherapy consisting of in vitro expanded myelin-reactive T-cells manufactured against up to six immunodominant peptides derived from three myelin antigens: myelin binding protein, myelin oligodendrocyte glycoprotein, and proteolipid protein. Autologous T-cell immunotherapy has been suggested to deplete or regulate the pathogenic myelin-reactive T cells (MRTCs) that maintain autoimmune processes within the CNS of patients with MS. Treatment procedure includes a collection of blood from the MS patient and expansion of MRTCs from the blood. MRTCs are formulated and attenuated by irradiation before returning the final product to the clinical site for subcutaneous administration to patients. A Phase 2b placebo-controlled study was conducted in 150 subjects with RRMS and CIS. Although safe, Tcelna showed no statistically significant clinical or radiological benefit. [194] A phase 2 randomised trial - Abili-T - was carried out and concluded in 183 patients with SPMS, but the publication of the results is pending.

4 Future strategies for SPMS therapeutics

Disability progression in MS is a continuous and slow process that can take years. Similarly, new drug discovery and testing can take up to 15 years with success not guaranteed. In order to expedite the finding of new treatments for SPMS, several ways have been proposed. [25,26,67] Population characteristics and outcome measures should be carefully chosen and be consistent with the main objectives that motivated the research. Innovative trial design or repurposing drugs are two ways to increasing efficiency and cutting costs of

drug discovery. Finally, drug efficacy can be increased by combining drugs with different mechanisms of action.

4.1 New trial designs

Large-scale long-term placebo-controlled parallel group trials, using a 1:1 ratio, have been used so far to assess efficacy drug in progressive MS. The efficiency of clinical trials in SPMS can potentially be increased by allowing a number of treatments to be tried concurrently. Adaptive seamless designs are feasible in SPMS. [144,146] Multistage or multiarm randomised trials have been successfully used in other medical research areas, such as oncology for some time.[195] In 1999, for example, Bauer and Kieser proposed an adaptive two-stage design for the situation of multiple treatments to be compared with a control within a single confirmatory trial.[196] Such a trial would allow for an interim analysis to determine early termination or continuation of the study towards a second stage. Adaptive design methods are also useful in the early phases of drug development because are dynamically informative.[197,198]

4.2 Drug repurposing

Drug repurposing - also known as drug repositioning or drug re-profiling - is the application of already approved drugs to new diseases.[199,200] It is advantageous because the repurposed drugs have already passed the trial stages assessing safety in humans, reducing time and costs of drug development.[201–204]

In the past, drug repositioning was merely a consequence of chance or unforeseen drug effects, whereas nowadays computational methods have been developed to predict new

targets for established drug or different drugs that act on the same target. [200,201,205] Structurally similar molecules can predict similar biological effects.[206–208] Molecular activities of drugs can be also inferred based on their side-effects, or predicted from human genome.[202,209]

Faissner and colleagues looked for repurposed drugs with neuroprotective potential targeting iron deposition in the CNS, which is thought to mediate mitochondrial dysfunction neurotoxicity in progressive MS. They showed that tricyclic antidepressants, antipsychotics, and indapamide might work in progressive MS. They also showed that clomipramine was able to suppress or improve EAE. [210]

Vesterinen and colleagues developed an evidence based framework to select oral repursposed neuroprotective drugs to be tested in SPMS.[211] They found at least seven agents with putative neuroprotective properties. Three of these agents are under investigation in the MS-SMART trial and one has been successful in the SPRINT-MS study.[146,212]

4.3 Combination therapy

Combination therapy is widely used in medicine, including in the treatment of immune disorders, such as rheumatoid arthritis. The rationale for the use of combination therapy in MS, as highlighted by Conway and Cohen, is supported by the different mechanisms of action of the various available DMTs that can also have additive or synergistic efficacy. [213] Combination therapy has pros and cons, and drugs with different mechanisms of action can target different aspects of the disease pathogenesis, which is complex and heterogeneous,

but can also have additive side effects. [214] Some attempt at combination therapy has been done, but no convincing results have been found.[215–218]

Consistent with the rationale of combining immunomodulators with distinct mechanism of action, other combinations have obtained additive or synergistic effects in preclinical studies, showing a positive effect of combining vitamin D and interferon-β. The combination of anti-inflammatory and neuroprotective agents has also been tried in small studies such as the phase 2 trial combining intramuscular interferon-β 1a with riluzole or the ones combining minocycline and interferon-β or glatiramer acetate in RRMS [139,155,213]. The CombiRx trial, combining interferon-β 1a and glatiramer acetate, enrolled more than a thousand of patients with RRMS. Whereas the combination therapy did not produce a significant clinical benefit, there was evidence of superiority of the combination therapy over single arm treatment in reducing new lesion activity and accumulation of total lesion volumes. [215]

5. Conclusions

Studies in progressive MS have been increasing over the past two decades and there are many investigational products currently in the pipeline for both SPMS and PPMS (Table 1-5). With the ORATORIO trial, ocrelizumab represents the first drug that has shown some evidence of efficacy in PPMS. More recently, also the EXPAND trial has provided evidence of efficacy of siponimod in SPMS. [219,220] Ocrelizumab and siponimod reduced the worsening of disability over time in PPMS and SPMS respectively, but whether this effect is directly due to an interference with neurodegeneration or mediated by an anti-inflammatory effect is still debated.[221] New evidence from immunology and pathology

are changing our understanding of MS, which is no longer felt as a two-stage disease but rather a *continuum*, where both inflammation and neurodegeneration are contemporarily present at any moment in the course of the disease. [16,222] The EXPAND and ORATORIO trials suggest a greater therapeutic effect in patients with relative short disease duration, younger age and signs of baseline activity.

As we have written in this review, treatments in progressive MS will probably include an anti-inflammatory approach, which is likely to be combined with myelin repair and neuroprotection. The use of repurposed drugs and combination therapy looks promising. Targeting specific study populations with appropriate outcome measures and efficient trial designs is essential to speed up the discovery of new pharmacotherapies for SPMS. [25–28]

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Table 1 Phase 2 and 3 Trials concluded in progressive MS over the last 5 years.

Drug(s)	Study Title	Phase	Study design (comparator)	Subjects	Primary endpoint	Time frame	Study completion	Results	NCT number	Reference
Biotin (MD1003)	Effect of MD1003 in Spinal Progressive MS (MS-SPI)	3	RCT (placebo)	99 SPMS 55 PPMS	EDSS T25FWT	2y	2016	**Positive**	NCT02220933	Tourbah et al. [166]
Erythropoietin (rhEPO)	The Effects of Erythropoietin on Clinical Disability and Brain Pathology in PwPMS (EPO-ProgMS)	2	RCT (placebo)	34 SPMS 18 PPMS	MGD 9-HPT TMT-B	48w	2013	Negative	NCT01144117	Schreiber et al. [116]
Fingolimod (FTY720)	FTY720 in PwPPMS (INFORMS)	3	RCT (placebo)	969 PPMS	EDSS T25FWT 9-HPT	3y	2015	Negative	NCT00731692	Lublin et al.[223]
Fluoxetine	Fluoxetine in Progressive Multiple Sclerosis (FLUOX-PMS)	2	RCT (placebo)	72 SPMS 55 PPMS	T25FWT 9-HPT	2y	2016	Negative	NCT N/A EudraCT:2011 -003775-11	Cambron et al. [224,225]
Ibudilast (MN-166)	Safety, Tolerability and Activity Study of Ibudilast in PwPMS (SPRINT-MS)*	2	RCT (placebo)	121 SPMS 134 PPMS	MRI-BVC	3y	2017	**Positive**	NCT01982942	Fox R et al. and Naismith R et al. Congress Proceedings [130,131]
Idebenone	Double Blind Placebo-Controlled Phase I/II Clinical Trial of Idebenone in Patients with PPMS (IPPoMS)*	1/2	RCT (placebo)	85 PPMS	CombiWISE [226]	2y	2018	Negative	NCT00950248	Santhera Press Release [118]
Laquinimod	A Phase 2 Clinical Study in PwPPMS to Assess the Efficacy, Safety and Tolerability of Two Oral Doses of Laquinimod Either of 0.6 mg/Day or 1.5mg/Day as Compared to Placebo (ARPEGGIO)*	2	RCT (placebo)	374 PPMS	MRI-BVC	48w	2017	Negative	NCT02284568	Active Biotech Press Release [123]
Lipoic acid	Lipoic Acid for SPMS	2/3	RCT (placebo)	54 SPMS	MRI-BVC	2y	2015	**Positive**	NCT01188811	Spain et al. [227]
Lithium	A Pilot Trial of Lithium in PMS*	1/2	Crossover RCT (placebo)	20 PMS	MRI-BVC	2y	2015	Negative	NCT01259388	Rinker et al. Congress Proceedings [125]
Methylprednisolone	Cyclic Oral Methylprednisolone Trial in MS (COMTiMS)	2	Open label	15 SPMS 15 PPMS	Osteopontin	60w	2013	Negative	NCT01305837	Ratzer et al[228]
MIS416	A Phase 2B Randomised, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of MIS416 in the Treatment of PwSPMS*	2	RCT (placebo)	93 SPMS	Neuromuscular function	1y	2017	Negative	NCT02228213	Immunotherapeutics Press Release [229]
Natalizumab	Natalizumab Treatment of PMS (NAPMS)	2	Open label	12 SPMS 12 PPMS	Osteopontin	60w	2012	**Positive**	NCT01077466	Christensen et al [230]
Natalizumab	A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in PwSPMS (ASCEND)	3	RCT (placebo)	889 SPMS	EDSS T25FWT 9HPT	96w	2016	Negative	NCT01416181	Kapoor et al [231]
Ocrelizumab	A Study of Ocrelizumab in PwPPMS (ORATORIO)	3	RCT (placebo)	732 PPMS	EDSS	120w	2015	**Positive**	NCT01194570	Montalban et al.[232]

Polyphenon E	Safety and Neuroprotective Effects of Polyphenon E in MS; Phase II (POEMS)	2	RCT (placebo)	11 RRMS 0 SPMS	MRS-NAA	1y	2013	Terminated (liver toxicity)	NCT01451723	Lovera et al.[126]
Rituximab (IT)	Double Blind Combination of Rituximab by Intravenous and Intrathecal Injection Versus Placebo in Patients with Low-Inflammatory Secondary Progressive Multiple Sclerosis (RIVITaLISe)	1/2	RCT (placebo)	44 li-SPMS	CSF CXCL13 CSF BAFF	3m	2015	Terminated (lack of efficacy)	NCT01212094	Komori M et al. [233]
Siponimod (BAF312)	Exploring the Efficacy and Safety of Siponimod in PwSPMS (EXPAND)	3	RCT (placebo) (blind phase)	1651 SPMS	EDSS	3y	2017	**Positive**	NCT01665144	Kappos et al.[234]
Sunphenon EGCG (Epigallocatechin-Gallat, EGCG)	Sunphenon in Progressive Forms of MS (SUPREMES)	2/3	RCT (placebo)	60 PMS	MRI-BVC	3y	2016	Completed. Results not reported	NCT00799890	NA
Tcelna (imilecleucel-T)	Study of Tcelna (Imilecleucel-T) in SPMS (Abili-T)*	2	RCT (placebo)	183 SPMS	MRI-BVC	2y	2016	Negative	NCT01684761	Opexa Therapeutics Press Release [235]

For the studies marked with an asterisk (*) full publication is pending (last checked date 03/04/2018) and preliminary results from conference proceedings or announcement press releases are reported. d= days. EDSS= expanded disability status scale. IT= intrathecal. li-SPMS= low inflammatory secondary progressive multiple sclerosis. m= months. MGD= maximum gait distance. MRI-BVC= magnetic resonance imaging-brain volume change. MRS-NAA= magnetic resonance spectroscopy-n-acetyl aspartate. A= not applicable. N/A= not applicable. NFL= neurofilament. rfSPMS= relapse free secondary progressive multiple sclerosis. RCT= randomised controlled trial. MS= multiple sclerosis. PMS= progressive multiple sclerosis. PPMS = primary progressive multiple sclerosis. SPMS= secondary progressive multiple sclerosis. T25FWT= timed 25-foot walking test. TMT-B= Trail Making Test - part B. w= week. y= year. 9HPT= 9-hole peg test (clinical trials have been searched on https://clinicaltrials.gov, last accessed date 03/04/18; the FLUOX-PMS trial is not present in the registry of clinicaltrials.gov, but it is registered with Eudra-CT).

Table 2 Phase 2 and 3 clinical trials in RRMS or acute ON investigating agents with a potential role in SPMS.

Drug(s)	Title	Phase	Study design (comparator)	Subjects	Primary endpoint	Time Frame	Study completion	Results	NCT number	Reference
Completed										
Clemastine	Assessment of Clemastine Fumarate as a Remyelinating Agent in Multiple Sclerosis (ReBUILD)	2	Crossover RCT (placebo)	50 acute ON	FFVEP	5m	2016	**Positive**	NCT02040298	Green AJ et al. [169]
GSK239512	Study to Assess Whether GSK239512 Can Remyelinate Lesions in Subjects with Relapsing Remitting Multiple Sclerosis	2	RCT (placebo)	131 RRMS	GELs Delta MTR	48w	2014	Negative	NCT01772199	Schwartzbach et al. [157]
Opicinumab (+ Interferon-β 1a)	Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BIIB033 in Participants with Relapsing Forms of MS When Used Concurrently with Avonex (SYNERGY)	2	RCT (placebo)	330 RRMS 88 RSPMS	EDSS T25FWT 9HPT	72w	2016	Negative	NCT01864148	Cadaviv et al. [236]
Phenytoin	Neuroprotection with Phenytoin in Optic Neuritis	2	RCT (placebo)	92 acute ON	RNFL	6m	2015	**Positive**	NCT01451593	Raftopoulos R et al. [143]
Ongoing										
Clemastine	Assessment of Clemastine Fumarate as a Remyelinating Agent in Acute Optic Neuritis (ReCOVER)	2	RCT (placebo)	30 acute ON	FFVEP	9m	2018	Recruiting	NCT02521311	*NA*
Mesenchymal Stem Cells	MEsenchymal StEm Cells for Multiple Sclerosis	1/2	Crossover RCT (placebo)	12 MS	Safety GELs	24w	2018	Recruiting	NCT02403947	*NA*
Opicinumab (+ DMT)	Efficacy and Safety of BIIB033 (Opicinumab) as an Add-on Therapy to Disease-Modifying Therapies (DMTs) in Relapsing Multiple Sclerosis (MS) (AFFINITY)	2	RCT (placebo)	240 RRMS	Response score.	72w	2020	Recruiting	NCT03222973	*NA*
Quetiapine	Safety and Tolerability of Quetiapine in Multiple Sclerosis	1/2	Open Label	36 MS	Toxicity	4w	2017	Recruiting	NCT02087631	*NA*
Rituximab Glatiramer Acetate	Comparison of Clinical Effects of Rituximab and Glatiramer Acetate in Active Progressive Multiple Sclerosis Patients	2/3	Open label	60 a-SPMS	ARR	1y	2019	Not yet recruiting	NCT03315923	*NA*

ARR= annualised relapse rate. a-SPMS= active secondary progressive multiple sclerosis. d=days. EDSS= expanded disability status scale. FFVEP= full field visual evoked potentials. GELs= gadolinium enhancing lesions. m= months. MRI-BVC= magnetic resonance imaging-brain volume change. MRS-NAA= magnetic resonance spectroscopy-n-acetyl aspartate. MTR= magnetic transfer ratio. NFL= neurofilament. ON= optic neuritis. RCT= randomised controlled trial. MS= multiple sclerosis. NA= not applicable. RRMS = relapsing-remitting multiple sclerosis. RSPMS= relapsing secondary progressive multiple sclerosis. RNFL= retinal nerve fibre layer. T25FWT= timed 25-foot walking test. w= weeks. y= years. 9HPT= 9-hole peg test. Response Score is a composite score including EDSS, T25FWT, 9-HPT in the dominant hand and 9HPT in the non-dominant hand. (clinical trials have been searched on https://clinicaltrials.gov, last accessed date 03/04/18).

Table 3 Ongoing Phase 2 and 3 clinical trials of agents with putative immune-modulation properties in progressive MS.

Drug(s)	Title	Phase	Study design (comparator)	Subjects (estimated)	Primary endpoint(s)	Time frame	Study completion	Status	NCT number
Dimethyl Fumarate*	Dimethyl Fumarate Treatment of PPMS (FUMAPMS)	2	RCT (placebo)	90 PPMS	NFL light chain	48w	2019	Recruiting	NCT02959658
Glatiramer Acetate Depot	Safety and Efficacy of Monthly Long-acting IM Injection of 40 mg GA Depot in Subjects With PPMS	2	Open label	24 PPMS	Safety	56w	2019	Recruiting	NCT03362294
Hydroxychloroquine	Hydroxychloroquine in PPMS	2	Open label	35 PPMS	T25FWT	18m	2020	Recruiting	NCT02913157
Masitinib	A Phase 3 Study to Compare Efficacy and Safety of Masitinib to Placebo in the Treatment of Patients with Primary Progressive or Relapse-free Secondary Progressive Multiple Sclerosis	2/3	RCT (placebo)	450 PPMS or rf-SPMS	EDSS	96w	2019	Recruiting	NCT01433497
NeuroVax™	A Study of NeuroVax™, a Novel Therapeutic TCR Peptide Vaccine for SPMS	2	RCT (IFA)	150 SPMS	EDSS	48w	2019	Not recruiting yet	NCT02149706
Ocrelizumab	A Study of Ocrelizumab in Participants with Primary Progressive Multiple Sclerosis	3	Open label (Extension phase)	Variable number PPMS		4y (max)	2021	Active not recruiting	NCT01194570
Rituximab	Intrathecal Rituximab in PMS (EFFRITE)	2	Open label	12 PMS	Osteopontin	180d	2017	Unknown	NCT02545959
Siponimod (BAF312)	Exploring the Efficacy and Safety of Siponimod in PwSPMS (EXPAND)	3	Open label (Extension phase)	Variable number SPMS	EDSS	3y	2023	Active not recruiting	NCT01665144

Drugs marked with an asterisk (*) may have additional neuroprotective properties. EDSS= expanded disability status scale. GEP= global evoked potential. IFA= Freund's Adjuvant. MRI-BVC= magnetic resonance imaging-brain volume change. NFL= neurofilaments. RCT= randomised controlled trial. MS= multiple sclerosis. NFL= neurofilament. PMS= progressive multiple sclerosis. PPMS = primary progressive multiple sclerosis. rf-SPMS= relapse free secondary progressive multiple sclerosis. SPMS= secondary progressive multiple sclerosis. T25FWT= timed 25-foot walking test. For the time frame, the following abbreviations have been used: d=days. m: month. w= week. y= year. (clinical trials have been searched on https://clinicaltrials.gov, last accessed date 03/04/18).

Table 4 Ongoing Phase 2 and 3 clinical trials of agents with putative neuroprotective properties in progressive MS.

Drug(s)	Title	Phase	Study design	Subjects (estimated)	Primary endpoint(s)	Time frame	Study completion	Status	NCT number
Andrographolides	Efficacy, Safety and Tolerability of Andrographolides Versus Placebo in Patients with Progressive Forms of MS	1/2	RCT (placebo)	68 PMS	MRI-BVC	2y	2017	Unknown	NCT02273635
Amiloride Fluoxetine Riluzole	MS Secondary Progressive Multi Arm Randomisation Trial (MS-SMART)	2	Multiarm RCT (placebo)	445 SPMS	MRI-BVC	96w	2018	Active, not recruiting	NCT01910259
Lipoic Acid	Lipoic Acid for Progressive MS	2	RCT (placebo)	118 PMS	T25FWT	2y	2021	Not yet recruiting	NCT03161028
Oxcarbazepine	Protective Role of Oxcarbazepine in MS (PROXIMUS)	2	RCT (placebo)	30 SPMS/PRR MS	NFL light chain	48w	2018	Recruiting	NCT02104661
Simvastatin	Multiple Sclerosis-Simvastatin Trial 2 (MS-STAT2)	3	RCT (placebo)	1180 SPMS	EDSS	182w	2023	Recruiting	NCT03387670

EDSS= expanded disability status scale. m= months. MRI-BVC= magnetic resonance imaging-brain volume change. MS= multiple sclerosis. NFL= neurofilament. PMS= progressive multiple sclerosis. PRRMS= progressive relapsing-remitting multiple sclerosis. PPMS = primary progressive multiple sclerosis. RCT= randomised controlled trial. SPMS= secondary progressive multiple sclerosis. T25FWT= timed 25-foot walking test. w= week. y= year. (clinical trials have been searched on https://clinicaltrials.gov, last accessed date 03/04/18)

Table 5 Ongoing Phase 2 and 3 clinical trials of agents with putative regenerative properties in progressive MS.

Drug(s)	Titke	Phase	Study design	Subjects (estimated)	Primary endpoint(s)	Time frame	End	Status/Results	NCT number
ACTH*	ACTH in Progressive Forms of MS	2	RCT (placebo)	100 PMS	T25FWT	3y	2022	Recruiting	NCT01950234
ABMT* (IV)	Assessment of Bone Marrow-derived Cellular Therapy in PMS (ACTiMuS)[237]	2	Crossover RCT (placebo)	60 SPMS 20 PPMS	GEP	2y	2018	Recruiting	NCT01815632
Biotin (MD1003)	Effect of MD1003 in PMS (SPI2)	3	Placebo	600 PMS	EDSS T25FWT	15m	2019	Recruiting	NCT02936037
Domperidone	Domperidone in SPMS	2	Open label	62 SPMS	T25FWT	1y	2020	Recruiting	NCT02308137
Mesenchymal stem cells	Optimal Administration Mode of Autologous Mesenchymal Bone Marrow Stem Cells in Active and Progressive Multiple Sclerosis	2	Randomised (different administration)	36 PMS	MRI-BVC Immunologic al Response	1y	2018	Recruiting	NCT02166021
Mesenchymal Stem Cell-derived Neural Progenitors	Intrathecal Administration of Autologous Mesenchymal Stem Cell-derived Neural Progenitors (MSC-NP) in Progressive Multiple Sclerosis	2	Crossover RCT (placebo)	50 PMS	EDSS-Plus	27m	2023	Recruiting	NCT03355365

Drugs marked with and asterisk (*) may have also additional immunemodulation properties. ABMT= autologous bone marrow transplantation. ACTH= adrenocorticotropic hormone. EDSS= expanded disability status scale. GEP= global evoked potential. IV= intravenous. m= months. MRI-BVC= magnetic resonance imaging-brain volume change. RCT= randomised controlled trial. MS= multiple sclerosis. PMS= progressive multiple sclerosis. PPMS = primary progressive multiple sclerosis. SPMS= secondary progressive multiple sclerosis. T25FWT= timed 25-foot walking test. y= years. (clinical trials have been searched on https://clinicaltrials.gov, last accessed date 03/04/18).