PROGRESSIVE MULTIPLE SCLEROSIS: PROSPECTS FOR DISEASE THERAPY, REPAIR, AND RESTORATION OF FUNCTION

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Summary

Multiple sclerosis is a major cause of neurologic disability, which accrues predominantly during progressive forms of the disease. While development of multifocal inflammatory lesions is the underlying pathologic process in relapsing-remitting multiple sclerosis, the gradual accumulation of disability that characterizes progressive multiple sclerosis appears to result from more diffuse immune mechanisms and neurodegeneration. As a result, the13 anti-inflammatory medications with regulatory approval to treat relapsing-remitting multiple sclerosis have little or no efficacy in progressive multiple sclerosis without inflammatory lesion activity. Thus, effective therapies for progressive multiple sclerosis that prevent worsening, reverse damage, and restore function represent major unmet needs. This review summarizes the current status of therapy for progressive multiple sclerosis and outlines prospects for the future.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. The global prevalence of MS was estimated at 2·3 million in 2013,[1] an increase of 0·2 million from five years earlier. This prevalence is likely an underestimate and does not fully account for the number of patients with MS in large Asian countries. Approximately 15% of patients begin with a progressive disease course from onset, termed primary progressive MS (PPMS); approximately 70% develop progression 10–15 years after an initial relapsing-remitting (RR) course, termed secondary progressive MS (SPMS). Thus, at least 1·3 million people have progressive MS.

Disability in MS accrues predominantly in the progressive forms of the disease, creating a significant healthcare burden at the individual, family, and community levels. Although substantial progress has been made in the treatment of RRMS – 13 medications currently have regulatory approval – development of therapies that prevent or reverse progression has been slower. International efforts such as the International Progressive MS Alliance are increasing the focus on PMS and identifying specific research areas to target.[2] This review summarizes the current status of therapy for progressive MS and outlines prospects for the future.

Current understanding of the pathogenesis of progressive multiple sclerosis

The pathogenic mechanisms underlying progression are incompletely understood. Moreover, since the division 25 years ago of what previously was called chronic progressive MS into PPMS and SPMS, it remains uncertain whether they represent overlapping or distinct entities.[3] Patients with PPMS and SPMS both exhibit gradually worsening disability, most often motor impairment with a pattern suggesting a myelopathy but also may have progressive hemiparesis, ataxia, visual dysfunction, or cognitive impairment. While the onset of progression commonly occurs at age 40-50 in both groups, SPMS follows an initial RR phase typically lasting 10–15 years. Patients with PPMS have an equal gender balance, while SPMS more commonly affects

women. In patients with radiologically isolated syndrome (MRI findings typical of MS without clinical manifestations), a small proportion have clinical conversion manifested as gradual progression of disability.[4] The proportion, demographics, gender balance, clinical characteristics, and frequency of cord lesions are similar to those of PPMS in the overall MS population. The current consensus is that PPMS is biologically part of the MS spectrum, and the clinical, imaging, and pathological differences between PPMS and SPMS are more relative than absolute. Therefore, in much of this review, PPMS and SPMS will be discussed together as progressive MS (PMS).

The pathological mechanisms causing tissue damage in RRMS and PMS overlap but differ quantitatively. In the early stages, MS pathology is dominated by focal inflammatory lesions with perivenular accumulation of T and B lymphocytes, blood-brain barrier disruption, demyelination, and acute axonal transection.[5] Although focal lesions sometimes develop in PMS, new lesion activity becomes less frequent over time. In contrast, diffuse pathology in grossly normal-appearing white and gray matter with microglial activation and neurodegeneration are more prominent.[6] These features are found in early MS as well, but increase with age and disease duration.

The clinical importance of gray matter pathology involving cortex, deep structures, cerebellum, and spinal cord in PMS is increasingly recognized.[7] Several types of cortical lesions have been distinguished: leukocortical (subcortical lesions affecting adjacent white and gray matter), intracortical, and subpial lesions (spanning long distances in the subpial ribbon and extending from the surface to cortical layers II or IV).[8] Cortical histopathology includes microglial activation, demyelination, neuritic transection, neuronal death, and reduced presynaptic terminals but tends not to include perivascular lymphocytic cuffs typical of white matter lesions.[8] Subpial lesions may be associated with meningeal infiltrates of T and B lymphocytes, plasma cells, and macrophages,[6] which in some cases of SPMS form structures resembling lymphoid

follicles.[9] The severity of cortical demyelination correlates with the extent of meningeal inflammation in PMS, suggesting a pathogenic role.[10]

A number of potential mechanisms are hypothesized to lead to neurodegeneration in PMS (Figure 1),[11] many of which are potential therapeutic targets. Demyelinated axons are abundant in longstanding MS and are hypothesized to be susceptible to chronic injury.[6] In addition to loss of myelin's structural and trophic support, chronic demyelination might permit increased exposure to toxic species in the microenvironment: inflammatory mediators, and reactive oxygen and iron species. In some demyelinated axons, saltatory nerve impulse conduction is replaced by continuous conduction, which restores function but increases energy demand and sodium accumulation in the axonal cytoplasm. Resultant reverse operation of sodium-calcium exchanger to restore ionic gradients could lead to cytoplasmic calcium accumulation, activation of calpains, and proteolysis of cytoskeleton. As discussed below, studies of sodium channel blockers had mixed results.[12,13] Although remyelination can be seen in some lesions, the failure of remyelination in other areas is hypothesized to cause axonal degeneration and disease progression. Thus, remyelination is a potential therapeutic goal. The abundance of oligodendrocyte precursors in some chronic lesions suggests that lack of such cells does not explain failure of remyelination.[14] Rather, the absence of factors necessary for successful remyelination or the presence of inhibitory factors is more likely responsible. This concept has important implications for potential repair-promoting strategies.

Axonal injury also is a major contributor to irreversible disability. This injury is believed to occur through a combination of acute inflammatory damage, degeneration of chronically demyelinated axons in white and gray matter, and antegrade and retrograde trans-synaptic degeneration due to distal axonal transection.[15] There is increasing evidence that mitochondrial dysfunction in axons results from impaired mitochondrial transport, susceptibility to oxidative injury, and mutations in mitochondrial DNA, all of which lead to impaired energy production and generation of reactive oxygen species. The net effect of these processes is accumulation of

various toxic species, increased cellular energy demand, failure of energy production, and virtual hypoxia resulting in neurodegeneration. Improved energy production is the proposed mechanism of action of high-dose biotin.[16]

Revised multiple sclerosis phenotype classification

Increasing recognition that relapses and MRI lesion activity occur in some patients with PMS, mainly in the early stages, led to recent revision of the phenotypic categories of PMS (Figure 2).[17] The new scheme still differentiates progression at disease onset (PPMS) from progression after an initial RR course (SPMS) but adds two qualifiers: presence or absence of clinical relapses or new MRI lesions ("active" or "not active"), and presence or absence of gradual worsening disability independent of relapses ("with progression" or "without progression"). These qualifiers are intended to be re-assessed over time, e.g. annually, with patients potentially changing category based on recent disease course.

The new classification will have significant benefits in recognizing two relatively separate facets of PMS – inflammatory lesion activity and gradual progression. The classification will be especially helpful for selection of informative clinical trial participants. As discussed below, the presence of recent relapses or active MRI lesions is an important determinant of efficacy in PMS of medications with predominantly anti-inflammatory effects. It is hoped that in the future, phenotypic classification will incorporate additional imaging and non-imaging biomarkers, genetic markers, and epigenetic factors to categorize patients more comprehensively.

Clinical measures of disability

Clinical outcome measures must take into account heterogeneous clinical manifestations, unpredictable course, and generally slow rate of worsening in PMS. The current measures address these issues in different ways.[18] The Kurtzke Expanded Disability Status Scale (EDSS) is based on the neurologic examination and assesses a range of neurological functions,

permitting comparison between individuals or groups on a 0–10 scale. Despite limitations, the EDSS is likely to continue to be used as a measure of MS-related disability. An alternative approach, the MS Functional Composite (MSFC), uses quantitative neuroperformance tests covering four neurologic domains – Timed 25-Foot Walk (T25FW, short-distance walking speed), Nine-Hole Peg Test (9HPT, upper extremity function), Sloan low contrast letter acuity (vision), and Paced Auditory Serial Addition Test or Symbol Digit Modalities Test (cognitive processing speed and sustained attention). Anticipated advantages of the MSFC compared to the EDSS are ease of administration, more meaningful contribution from several neurologic domains, improved reliability, and greater sensitivity in some populations. The Multiple Sclerosis Outcome Assessments Consortium comprising MS clinical researchers from academia and industry currently is working to develop the MSFC approach further and obtain formal regulatory qualification for use in MS trials.[19] The INFORMS trial of fingolimod in PPMS[20] employed a composite outcome measure combining EDSS, T25FW, and 9HPT. Although the trial did not demonstrate efficacy, the composite endpoint detected events in 69% of participants, more than its components.

A number of automated measurement devices to capture function in MS are under development. The MS Performance Test is a battery of quantitative neuroperformance assessments modeled after the MSFC designed for supervised or self administration using a suite of iPad® apps.[21] Several smartphone and wearable motion sensors have been developed, which provide the ability to measure community-based ambulation and physical activity. How such data can be used to assess therapies in clinical trials or to make therapeutic decisions in practice is unclear at present. Nevertheless, it is expected that MS disability assessment will undergo further refinement to include various performance measures. Methods for capturing large segments of data using the electronic medical record also will expand in the future.

The role of imaging in progressive multiple sclerosis

MRI is a key diagnostic tool in all forms of MS. In addition, because of the greater sensitivity of MRI compared to clinical outcomes, a standard approach in the development of anti-inflammatory therapies for RRMS employs MRI lesion activity in phase 2 trials to predict benefit on relapses in subsequent phase 3 trials.[22] Such a marker is lacking in PMS where lesion activity is less common than in RRMS and disability often worsens without lesion accrual. Moreover, due to its limited pathologic specificity, standard MRI does not appear to detect the pathologic processes that underlie disability progression. Several imaging approaches under development show promise to meet this need.

Brain volume measures

Whole brain atrophy, which reflects aggregate tissue injury, is more severe in PMS compared to RRMS, though the rate of volume loss is relatively constant over the course of the disease.[23] Whole brain atrophy correlates with physical[23] and cognitive[24] impairment. Treatment effects on brain atrophy predict effects on disability, at least in RRMS.[25] Methods for measuring whole brain volume are reasonably well established, and published sample size estimates for PMS trials based on whole brain atrophy are feasible.[26] The main disadvantage as a phase 2 trial outcome is the rather slow rate of change, prolonging trial duration. In addition, precise whole brain volume measurement is technically challenging and subject to significant biologic variability, making it difficult to implement in clinical practice.

Methods to detect gray matter pathology

Conventional MRI does not detect cortical lesions, an important site of MS injury. Specialized sequences like double inversion recovery[27] and ultra-high field (7 tesla) MRI[28] allow identification of some but not all cortical lesions. Because of the insensitivity of current techniques to demonstrate cortical pathology directly, some studies have measured cortical thickness or volume to quantify pathology indirectly. Cortical atrophy is prominent in PMS[29] and

correlates with physical[30] and cognitive[31] impairment. Atrophy of deep gray structures (thalamus, caudate, and hippocampus) also occurs in PMS and can be focal (presumably due to lesions) or more diffuse (presumably due to damage to afferent or efferent connections).[32,33] Like whole brain atrophy measures, regional atrophy measures require substantial image post-processing, making them more suitable for research studies than clinical practice.

"Advanced" MRI techniques

Several MRI techniques may provide improved pathologic specificity and, thus, better correlation with clinical disability: diffusion tensor imaging (DTI, which quantifies the three-dimensional diffusion of water),[34] magnetization transfer imaging (MTI, which quantifies tissue integrity through the interaction of protons bound to molecular structures and free water),[35] magnetic resonance spectroscopy (which quantifies tissue metabolites),[36] and techniques such as magnetic resonance fingerprinting.[37] These techniques can be applied to the whole brain, or selectively to gray or white matter lesions, or regions that appear normal on standard MRI. All of these techniques show promise but require further validation of their pathologic specificity.

Spinal cord imaging

Spinal cord atrophy correlates with clinical measures of disability.[38] Quantitative and more pathologically specific MRI measures of spinal cord are difficult due to low spatial resolution, pulsation artifact, cerebrospinal fluid partial volume averaging, and challenges in registration. Nevertheless, assessment of the spinal cord using DTI,[39] MTR,[40] and spectroscopy[41] may provide important insights in PMS.

Positron emission tomography

Positron emission tomography markers for activated microglia[42] and myelin[43] have been developed that potentially could assess disease status in PMS. This technique's principal shortcoming is its limited spatial resolution.

Optical coherence tomography

Optical coherence tomography is a rapid, non-invasive technique that provides high-resolution quantification of the retinal nerve fiber layer (the axons that extend to the optic nerve) and the corresponding neuronal cells bodies in the ganglion cell layer. These measures directly reflect the axonal integrity of the optic nerves and correlate with overall clinical disability[44] and brain MRI measures.[45]

Status of disease therapy for progressive multiple sclerosis

Anti-inflammatory strategies

Most medications approved for RRMS have been tested in PMS (Table 1). Interferon-β1 therapies were evaluated in SPMS shortly after their efficacy was demonstrated in RRMS. Although two trials were positive,[46,47] several others were negative.[48-50] Similarly, a phase 3 trial of glatiramer acetate in PPMS was negative.[51] Subsequent analysis found that trials enriched with participants with recent relapses and MRI lesion activity tended to demonstrate benefit from interferon-β1.[52] Similar results were observed with other anti-inflammatory therapies in PMS.

Fingolimod, a sphingosine 1-phosphate (S1P) receptor modulator, reduced relapses, MRI lesion activity, and brain volume loss in three phase 3 trials in RRMS.[53-55] Fingolimod readily enters the brain and has direct effects on several central nervous system cell types mediated by S1P receptors, suggesting it might be beneficial in PMS.[56] A phase 3 trial of fingolimod in PPMS demonstrated reduction in new MRI lesions but not the risk of confirmed disability worsening measured by a composite outcome that included EDSS, T25FW, and 9HPT.[20] These results

indicate that entry of a medication into the central nervous system and direct actions there do not ensure efficacy in PMS.

Another highly effective anti-inflammatory therapy, the anti-α_1 integrin monoclonal antibody natalizumab, was evaluated in a phase 3 trial in SPMS. Natalizumab therapy did not slow worsening of disability measured by a composite outcome similar to that used to test fingolimod, though benefit was seen on 9HPT.[57] The lack of benefit on progression of natalizumab, one of the more potent anti-inflammatory therapies for RRMS, underscores the importance of mechanism of action in determining efficacy.

Because of the potent efficacy of anti-CD20 monoclonal antibodies in RRMS, there is increased recognition of the multifaceted role of B lymphocytes in MS pathogenesis beyond antibody production.[58] In a phase 3 trial in PPMS, rituximab treatment slowed the change in lesion volume relative to placebo, but did not decrease the risk of confirmed disability progression.[59] In planned subgroup analyses, participants younger than 50 years and those with gadolinium-enhancing lesions at baseline showed benefit on disability progression. Based on those results, a humanized anti-B lymphocyte monoclonal antibody, ocrelizumab, was evaluated in PPMS. This phase 3 trial demonstrated that ocrelizumab reduced the risk of disability progression by 24%.[60] Importantly, this trial enrolled relatively young participants (mean age 44.6 years; maximum 55 years), with short disease duration (mean 6.4 years; maximum 15 years), and a relatively high proportion with gadolinium-enhancing lesions at baseline (26%). The subgroup with gadolinium-enhancing lesions at baseline appeared to have a greater reduction in risk of disability progression, though the difference was not significant.[61]

The different results obtained in PMS trials appear not to relate to differences in anti-inflammatory potency. Instead, the results suggest that those trials enrolling a study population with younger age, shorter disease duration, and more ongoing inflammatory lesion activity tend to demonstrate greater benefit. Conversely, older patients without lesion activity gain little if any benefit as a group. In addition to study population, mechanism of action also may be relevant,

although that requires further study. These observations provide valuable guidance for both the characteristics of participants to enroll in future trials and the choice of therapies to study in PMS.

Neuroprotective therapeutic strategies

The limited success of anti-inflammatory agents in treating PMS suggests that other therapeutic approaches, such as neuroprotective or repair-promoting strategies, will be necessary. A phase 2 study assessed the potential cytoprotective properties of simvastatin in SPMS.[62] Simvastatin produced a 43% reduction in whole brain volume loss and a slowing in disability worsening measured by EDSS (absolute difference in means of 0.25 points). Another trial utilized a repurposed sodium-channel blocker, phenytoin, to protect axons from acute inflammatory injury in acute optic neuritis.[12] Phenytoin treatment within two weeks of onset led to a 30% decrease in loss of retinal nerve fiber layer thickness relative to placebo. This success is in contrast to the negative results with another sodium channel blocker, lamotrigine, in slowing brain volume loss in SPMS.[13] This discrepancy may relate to a “pseudo-atrophy” effect seen in the first year of the lamotrigine study, which may have obscured a potential benefit. Similarly, the neuroprotective effects of cannabinoids observed in the laboratory were not confirmed in a trial of the synthetic cannabinoid, dronabinol in PPMS and SPMS. Treatment did not reduce disability worsening over three years.[63] The low progression rate in the placebo group decreased the ability of this study to demonstrate benefit.

Cellular energy metabolism appears to be abnormal in PMS[11] and is another potential therapeutic target. The vitamin biotin is a coenzyme for many essential carboxylases and, in high doses, is hypothesized to enhance cellular energy production with resultant improved axonal function, decreased neurodegeneration, and enhanced remyelination.[64] A placebo-controlled phase 3 trial evaluated whether high dose biotin (300 mg/day) improved disability in

SPMS and PPMS.[16] The study found that 13% of treated participants had improvement in measures of disability, compared to none in the placebo group.

Repair-promoting strategies

LINGO-1 is a protein expressed by oligodendrocytes and neurons that inhibits remyelination.[65] Treatment of patients with acute optic neuritis with the LINGO-1-blocking monoclonal antibody BIIB033 did not improve recovery of visual evoked potential latency, a measure of optic nerve conduction, in the primary analysis but was effective in a post-hoc "per-protocol" analysis.[66] Negative results of a phase 2 trial assessing whether BIIB033 improves disability in RRMS and SPMS (clinicaltrials.gov identifier NCT01864148) recently were announced.

Cell-based repair-promoting strategies have received much attention as a potential therapeutic approach in PMS. Oligodendrocyte progenitor cells (OPCs) can be isolated from fetal human brain and when injected intracerebrally into hypomyelinating shiverer mice, lead to widespread myelination and reversal of the clinical phenotype.[67] A phase 1 dose-escalation trial to evaluate the feasibility and safety of intracerebral injections of these cells in SPMS currently is planned.[68]

An intriguing related approach involves using OPCs[69] or OPC-like induced pluripotent stem cells[70] as the basis for high-throughput screening of already available drugs for their ability to stimulate remyelination. Molecules identified in the initial screens were further evaluated by increasingly stringent *in vitro* and *in vivo* testing, identifying the muscarinic antagonist benztropine, the antihistamine clemastine, the imidazole antifungal miconazole, and the topical steroid clobetasol as potential candidates for further testing. A pilot study of clemastine showed improvement on visual evoked potentials in participants with MS-related chronic optic neuropathy.[71]

Significant work has assessed mesenchymal stem cell (MSC) transplantation as a potential repair-promoting strategy in MS.[72] MSCs are pluripotent precursor cells that can be isolated

from bone marrow, adipose tissue, and numerous other tissues, and culture-expanded to purity. They exhibit numerous immunomodulatory, tissue-protective, and repair-promoting properties.[72] Following several preliminary studies in MS showing good safety and tolerability, the ongoing MESEMS phase 2 trial (clinicaltrials.gov identifier NCT01854957) should provide more definitive evidence concerning safety and efficacy. However, important methodological questions remain, including preferred source (bone marrow versus adipose tissue), cell production protocol to optimize yield and potency, whether the cells can be cryopreserved or need to be administered immediately, best route of administration (intravenous, intrathecal, or intra-arterial), appropriate dose and dosing schedule, and whether the cells should be derived from the patient (autologous) or someone without MS (allogeneic).[72]

Future directions

The largely disappointing results of studies of anti-inflammatory agents in PMS indicate that therapeutics that target other mechanisms will be necessary. One obstacle to development of such strategies is our incomplete understanding of the pathophysiology of progression. Therefore, the range of approaches under investigation remains relatively broad and without a clear pattern of success as yet. MS-SMART (clinicaltrials.gov identifier NCT01910259) is applying an adaptive trial design to evaluate three putative neuroprotective agents, amiloride, riluzole, and fluoxetine. A second significant obstacle is the lack of a validated phase 2 trial methodology that reliably predicts success of neuroprotective and repair-promoting strategies in phase 3 studies. Two general approaches have been utilized to date: recovery from an acute lesion involving an eloquent pathway (e.g. the optic nerve), or an imaging biomarker (e.g. whole brain atrophy). The eloquent pathway approach has the advantage of sensitivity, but the relevance to PMS of lessening damage or improving recovery from a focal acute inflammatory lesion is uncertain. Conversely, assessing whole brain or regional volume loss appears more likely to measure preservation of tissue integrity relevant to PMS but may be insufficiently

sensitive for a phase 2 trial. In addition to testing the efficacy of ibudilast in PPMS and SPMS, the SPRINT-MS trial (clinicaltrials.gov identifier NCT01982942) is evaluating the relative sensitivity of whole brain and regional atrophy measures, DTI, MTI, and OCT to detect neuroprotection for use in proof-of-concept clinical trials. At the present time, however, the population most likely to benefit from neuroprotective or repair-promoting strategies and the optimal trial design to demonstrate benefit have yet to be defined.

Restorative and rehabilitation approaches

Persons with PMS must manage increasing disability from a wide range of complex interacting symptoms, with impairments of gait, vision, and cognition considered the most relevant for those who have lived with MS for over 15 years.[73] Given the paucity of pharmacologic treatments for these symptoms, restorative and rehabilitation approaches form the mainstay of their management; highlighted as a key priority by the International Progressive MS Alliance.[2] While most studies of physiotherapy and multi-disciplinary rehabilitation have focused on RRMS, there is some evidence that these approaches are effective in improving ability and participation, and importantly health-related quality of life and coping skills in patients with PMS.[74] However, a recent systematic review found that, while 13 studies showed benefit in at least one outcome measure, all either were under-powered or had methodological issues.[74] Adequately designed clinical trials will be necessary to advance rehabilitation for PMS.

There is some evidence to suggest that exercise, incorporating endurance or resistance training, is feasible in MS,[75] and improving physical fitness benefits not only physical but also cognitive function.[76] Addressing the multiplicity of symptoms in PMS may require a combination of approaches and utilise a range of outcomes. A recent pilot trial used three forms of exercise and demonstrated benefit in both mobility and cognition.[77] Similarly, a recent study showed augmented benefit from combining exercise with symptomatic therapy.[78] For more disabled patients, use of robotics may be helpful.[79] Results for gait and balance training have been

encouraging, though trial sizes were relatively small. Some benefits also were seen for upper limb function weakness and incoordination.

Numerous studies have demonstrated neuroplasticity in MS, measured with functional imaging and, more recently, physiological techniques at the synaptic level.[80,81] There is a body of evidence suggesting that functional reorganisation following a relapse helps restore function. At a cellular level, synaptic plasticity appears to make an important contribution to recovery in MS. Long-term potentiation of synaptic transmission may functionally compensate for neuronal loss through increasing synaptic excitability of denervated neurons. This phenomenon has been demonstrated following relapse but not yet in progression. The challenge will be to incorporate approaches that target these mechanisms into active rehabilitation programmes. This issue is compounded in PMS by more limited cognitive and motor reserve.

Finally, management of PMS presents a number of other challenges. This population is older with increased likelihood of comorbidities.[82] Recognition and treatment of conditions such as musculoskeletal disorders, diabetes, cardiac disease, and respiratory dysfunction are necessary to maximise levels of ability and participation. In addition, awareness of the factors that lead to falls – inevitably associated with increasing disability and therefore more common in PMS – and preventative measures to avoid them, is essential.[83]

Over and above all of these approaches, embracing a holistic concept of wellness and encouraging lifestyle choices across physical, emotional, social, intellectual, occupational, and spiritual dimensions is a key element of a comprehensive management plan and one that is strongly advocated by people with MS.[84] This approach serves to underline the importance of self-management at all stages of MS.

Conclusions

The pathogenic mechanisms underlying acute relapses and progression differ, though both processes probably co-exist to varying degrees throughout the course of MS. Therapies

approved for RRMS have little or no benefit in PMS in the absence of ongoing inflammatory lesion activity. Therapies that prevent progression independent of acute inflammatory pathology are needed. Approaches to restore function, both through promoting tissue repair and improving function of damaged tissue, also are needed. Successful development of new therapies for PMS will require better understanding of the pathogenesis of progression and more sensitive clinical and imaging outcome measures.

Contributors

DO drafted the sections on phenotype classification and imaging, and provided modifications to the text in all other sections. AJT drafted the Introduction and sections on restorative and rehabilitation approaches, and provided modifications to the text in all other sections. RJF drafted the sections on disease and neuroprotective therapeutic strategies, and provided modifications to the text in all other sections. JAC drafted the sections on pathogenesis, measures of disability, and repair-promoting therapeutic strategies; provided modifications to the text in all other sections; and did the final editing before submission.

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Search strategy and selection criteria

This paper is based on the cumulative literature archives of the authors. In addition we searched PubMed for articles published in English up to April 1, 2016, with the search terms “multiple sclerosis”, “epidemiology”, “pathology”, “inflammation”, “neurodegeneration”, “demyelination”, “remyelination”, “outcome measures”, “magnetic resonance imaging”, “clinical trial”, “stem cell”, and “rehabilitation”, including only human and non-retracted publications.

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Table: Recent phase 3 clinical trials in progressive multiple sclerosis

Study	Population	Treatment arms (n)	Follow-up duration	Mean age (years)	Proportion of participants with gadolinium-enhancing lesions at baseline	Primary outcome	Results
Anti-inflammatory strategies							
ASCEND[57]	SPMS	natalizumab (439) placebo (448)	96 weeks	47.2	24%	6-month CDW based on a composite of EDSS, T25FW, and 9HPT	4% increase in CDW, OR=0.86, 95% CI [0.66-1.13], p=0.287

INFORMS[20]	PPMS	fingolimod (336) placebo (487)	3 years	49	13%	3-month CDW based on a composite of EDSS, T25FW, and 9HPT	5.05% reduction in CDW, HR=0.95, 95% CI [0.80-1.12], p=0.544
MAESTRO[85]	SPMS	MPB8298 (305) placebo (307)	2 years	49.9	N/A	6-month CDW based on EDSS	2.9% increase in CDW in DR2+/DR4+ subgroup, p=0.527 7.5% reduction in CDW in DR2-/DR4- subgroup, p=0.055

OLYMPUS[59]	PPMS	rituximab (292) placebo (147)	96 weeks	49.9	24.5%	3-month CDW based on EDSS	8.3% reduction in CDW, HR=0.77, 95% CI [0.55-1.09], p=0.144
ORATORIO[60]	PPMS	ocrelizumab (488) placebo (244)	120 weeks	44.6 years	26%	3-month CDW based on EDSS	24% reduction in CDW, HR=0.76, 95% CI [0.50-0.98], p=0.03
PROMiSe[51]	PPMS	glatiramer acetate (627) placebo (316)	36 months	50.4	14.1%	3-month CDW based on EDSS	HR=0.87, 95% CI [0.71-1.07], p=0.175
Neuroprotective or repair-promoting strategies							
CUPID[63]	PPMS SPMS	dronabinol (329) placebo (164)	36 months	52.2	N/A	6-month CDW based on EDSS, change in	0.1% reduction in CDW, HR=0.92, 95%

						MSIS-29 PHYS	CI [0.68-1.23], p=0.57
MS-SPI[16]	PPMS SPMS	biotin (103) placebo (51)	12 months	51.4	N/A	Proportion with disability improvement based on EDSS and T25FW at 9 months confirmed at 12 months	12% of participants in biotin arm improved compared with 0 in the placebo arm, p=0.005

9HPT = Nine-Hole Peg Test, CDW = confirmed disability worsening, CI = confidence interval, EDSS = Expanded Disability Status Scale, HR = hazard ratio, N/A = not applicable, MSIS-29 PHYS = physical impact subscale of the 29-item Multiple Sclerosis Impact Scale, OR = odds ratio, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, T25FW = Timed 25-Foot Walk

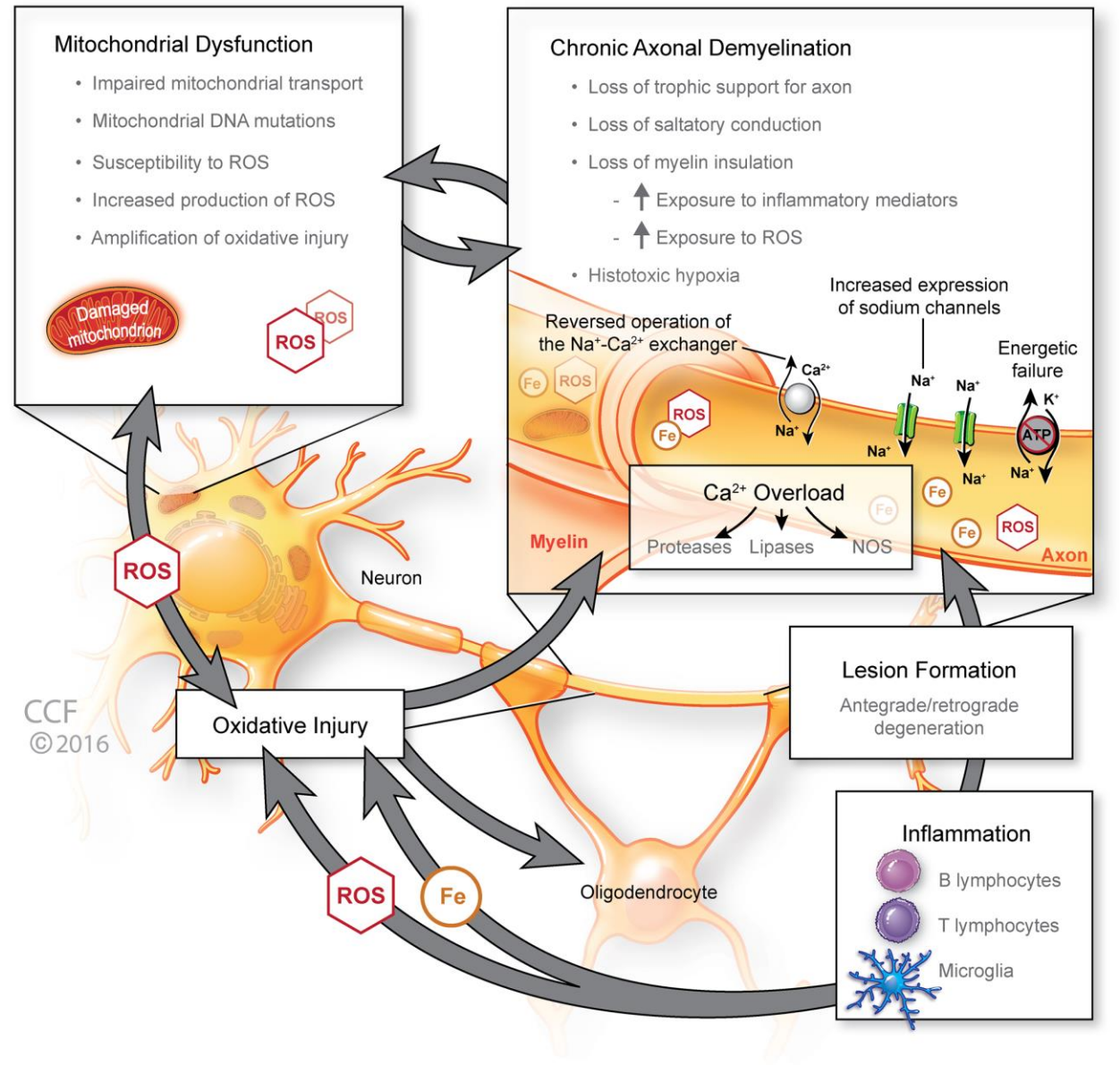
Figure legends

Figure 1: Pathogenesis of neurodegeneration in progressive multiple sclerosis

A large number of potential mechanisms have been hypothesized contribute to tissue injury in progressive multiple sclerosis (MS). Focal inflammatory demyelinating lesions are less common than in relapsing-remitting MS but do occur in progressive MS. Acute axonal transection may accompany inflammatory demyelination and leads to both antegrade and retrograde axonal degeneration. In addition to focal inflammatory lesions, diffusely distributed activated microglia are present and elaborate inflammatory mediators and reactive oxygen species (ROS), damaging numerous other cellular elements. Chronic demyelination is thought to result in loss of the insulating properties of myelin, increased exposure to inflammatory mediators and ROS, loss of structural and trophic support, and interruption of saltatory nerve impulse conduction. Up-regulation of sodium channel expression and insertion into the demyelinated axonal segment may restore function but with increased energy demand from replacement of saltatory nerve impulse conduction by continuous conduction. Energy failure and insufficiency of the sodium-potassium adenosine triphosphate pump leads to reverse operation of the sodium-calcium exchanger leads to cytoplasmic calcium accumulation. Calcium overload results in activation of calpains, proteases, lipases, and nitric oxide synthase leading to damage to of the axonal cytoskeleton and membrane. Dysfunction of axonal mitochondria results from impaired mitochondrial transport from the nucleus, oxidative injury, and mutations in mitochondrial DNA may lead to impaired energy production and further generation of ROS. Finally release of iron from damaged myelin and oligodendrocytes may lead to accumulation of toxic iron species. The proposed net result is neurodegeneration due to direct effects of toxic mediators, increased cellular energy demand, failure of energy production, and virtual hypoxia.

Figure 2: Categorization of patients with progressive multiple sclerosis

Progressive multiple sclerosis is defined by the presence at some time of gradual worsening in the absence of (or between) relapses. Clinically, primary progressive and secondary progressive multiple sclerosis (MS) are distinguished based on whether there is progression from disease onset or whether it follows a relapsing-remitting course, respectively. Patients with both forms of progressive MS are further categorized based on the presence or absence clinical relapses or new MRI lesions (“active” or “not active”) and of gradual worsening disability independent of relapses (“with progression” or “without progression”) in a preceding period of time (e.g. one year). An individual patient may move between these categories over time.


Mitochondrial Dysfunction
• Impaired mitochondrial transport
• Mitochondrial DNA mutations
• Susceptibility to ROS
• Increased production of ROS
• Amplification of oxidative injury
Damaged mitochondrion
ROS
Chronic Axonal Demyelination
• Loss of trophic support for axon
• Loss of saltatory conduction
• Loss of myelin insulation
- Exposure to inflammatory mediators
- Exposure to ROS
• Histotoxic hypoxia
Reversed operation of the Na+-Ca2+ exchanger
Increased expression of sodium channels
Energetic failure
Ca2+ Overload
Proteases Lipases NOS
Myelin
Axon
Neuron
Oxidative Injury
Lesion Formation
Antegrade/retrograde degeneration
Inflammation
B lymphocytes
T lymphocytes
Microglia
Oligodendrocyte
Fe
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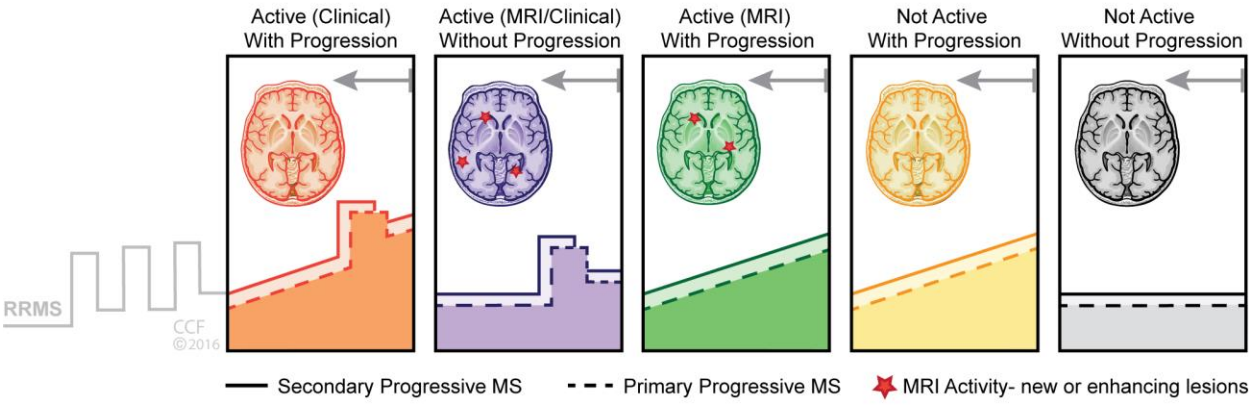
Active (Clinical) With Progression
Active (MRI/Clinical) Without Progression
Active (MRI) With Progression
Not Active With Progression
Not Active Without Progression
RRMS
CCF ©2016
Secondary Progressive MS
Primary Progressive MS
MRI Activity- new or enhancing lesions