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Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Approaches to Remyelination Therapies in Multiple Sclerosis

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Abstract

Purpose of review While there are a growing number of therapies targeting relapse prevention in multiple sclerosis (MS), there are no approved therapies promoting remyelination. Understanding endogenous myelin formation, remyelination strategies, pre-clinical models, and clinical outcomes is essential to the interpretation of current and future clinical trials of remyelinating agents.
Recent findings Several recent clinical trials of remyelination therapies, including opicinumab, clemastine, and GSK239512, showed negative or modest results. These results could highlight challenges translating pre-clinical studies into subjects with MS and current strategies to measure remyelination.
Summary Current approaches to remyelination include (1) blocking inhibitors of remyelination, (2) improving the clearance of myelin debris, (3) increasing the number of oligodendrocyte precursor cells (OPCs), and (4) stimulating OPC differentiation. To date, no therapies have led to robust remyelination. Future efforts to promote remyelination will likely require a combination of these mechanistic strategies.

Introduction

Multiple sclerosis (MS) is the most common non-traumatic cause of disability in young adults. In MS, demyelination with progressive failure of remyelination is thought to lead to axonal degeneration and permanent disability. While endogenous remyelination occurs, it is often incomplete and fails progressively over time. Therefore, clinicians and researchers are increasingly focused on developing novel therapies to promote remyelination. This article provides a review of translational research as a framework for understanding current and future remyelination trials.

Myelin formation

Central nervous system (CNS) myelination begins in early embryonic development. Pluripotent stem cells give rise to oligodendrocyte precursor cells (OPCs) under the control of multiple regulatory molecules, including sonic hedgehog and fibroblast growth factor (Fig. 1). OPCs then migrate from the ventricular zone throughout the CNS under the control of both chemo-attractant and chemo-repellant signals. OPCs undergo proliferation and maturation before entering terminal differentiation and can then myelinate axons. Once initiated, myelination can occur very rapidly. Therefore, the timing of OPC maturation is tightly regulated by both promoters (miRNA-219 and miRNA-338 [1]) and inhibitors (such as Jagged, CTCG, and PSA-NCAM) [2]. Mature OPCs travel along blood vessels and extend and retract cellular processes in order to identify axons [3, 4•]. Following this, oligodendrocytes wrap axons with concentric rings of myelin formed from an extension of the plasma membrane. Many factors impact myelination including axonal diameter [5] and OPC density [6]. In addition, axonal expression of proteins may influence oligodendrocytes: experiments in transgenic mice demonstrate that axonal expression of neuregulin, a class of proteins responsible for embryogenesis, influences the thickness of the myelin sheath [7]. The exact mechanism by which myelin wraps axons is still unknown and remains an area of scientific interest.

Importantly, in the adult CNS, remyelination can occur following demyelination. The process of remyelination appears to recapitulate developmental myelination, with OPC migration into an area of demyelinated axons, differentiation into premyelinating oligodendrocytes, and formation of myelin by mature oligodendrocytes (see Fig. 1).

Role of myelin

Myelin is essential in the CNS. The compacted ensheathment by myelin increases the electrical resistance of axons while decreasing the overall capacitance. Formation of unmyelinated nodes, with ionic channels in between the myelinated intermodal regions, allows for rapid saltatory conduction of action potentials along myelinated axons [2]. Therefore, myelin is credited as a key factor in the successful evolution from invertebrate to vertebrate species [8, 9]. The compacted myelin also provides structural integrity and protection to the underlying axon. In addition to these mechanical characteristics,

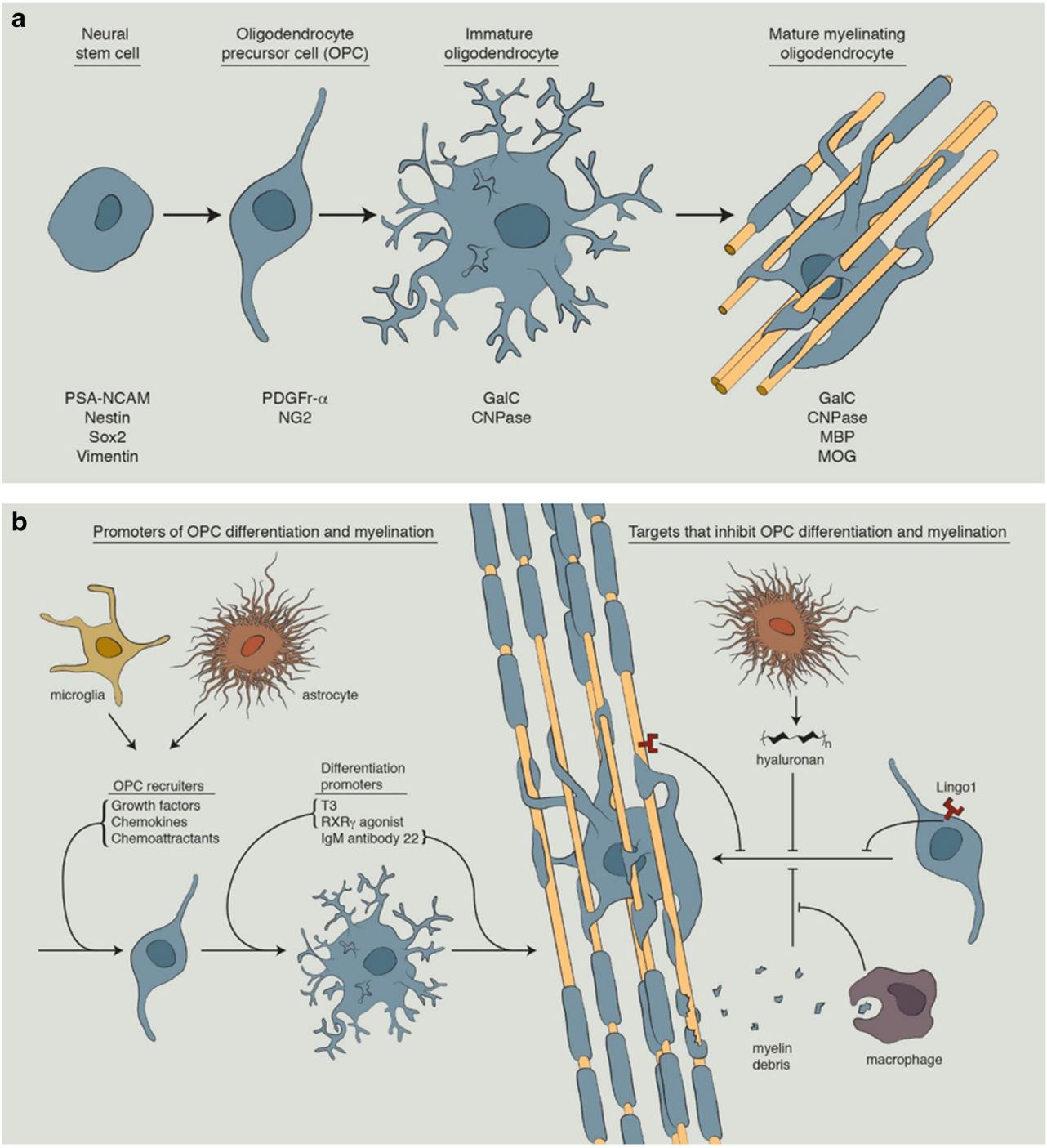

Fig. 1. Oligodendrocytes in remyelination. **a** Neural stem cells give rise to OPCs which then form myelinating oligodendrocytes. Key cellular markers for each developmental stage are shown. **b** Remyelination is tightly regulated by promoters (left) and inhibitors (right) of OPC differentiation. Several of these mediators are being studied as potential targets for remyelination therapies (from Hartley MD, Altowaijri G, Bourdette D. Remyelination and multiple sclerosis: therapeutic approaches and challenges. Curr Neurol Neurosci Rep. 2014; Vol 14, Issue10, reprinted with permission from Springer Nature).

oligodendrocytes provide dynamic metabolic support to axons. Myelin contains a complex network of microtubules which allow active transport of proteins to the neuron [10]. Recent work also demonstrates that oligodendrocytes have enriched glucose transporter (GLUT) and monocarboxylate transporters (MCTs), which help meet the high metabolic demand of axons. In animal models, disruption of lactate transporter MCT1 results in widespread axonal damage and neuronal death [11]. Reduced expression of these transporters has been identified in MS and other neurodegenerative diseases. Nijland et al.'s post-mortem analysis of MS brain tissue showed a marked reduction of GLUTs and MCTs in brain regions with chronic demyelination and axonal loss [11, 12]. Thus, the myelin sheaths synthesized and maintained by oligodendrocytes play a critical role in the function and long-term health of axons.

Consequences of demyelination

Relapsing-remitting MS is characterized by intermittent, acute, and focal inflammatory lesions that result in demyelination of axons and, to a lesser extent, axotomies. During a clinical relapse, an acute inflammatory lesion, or active plaque, forms in clinically eloquent areas of in the brain, spinal cord, or optic nerves. Histologically, the active plaque contains an influx of immune cells with parenchymal edema and focal loss of myelin [13]. This inflammatory demyelination interrupts neuronal signal transduction, resulting in focal neurologic dysfunction, known as a clinical relapse. Over subsequent weeks, clinical symptoms improve. Short-term improvement results from resolution of acute inflammation and restoration of the blood-brain barrier (BBB). Longer term improvement occurs with reorganization of Na^+ channels to facilitate signal transduction along the demyelinated axon [14] and remyelination. Despite repair, there is lasting damage to the underlying tissue. Chronic plaques commonly show variable degrees of chronic inflammation, gliosis, demyelinated axons, and variable axonal loss [15]. In early relapsing disease, there is a correlation between inflammatory disease activity and axonal damage. In chronic lesions, however, axonal injury continues independent of inflammation [16]. This neurodegeneration results in whole brain atrophy and contributes to progressive clinical disability [17].

Endogenous remyelination

Endogenous remyelination occurs in both acute and chronic phases of MS. When successful, remyelination restores axonal signaling and provides structural integrity to axons [15, 18]. However, remyelination is heterogeneous; some patients have robust remyelination while others have virtually no evidence of neuronal repair. In a review of over 300 MS lesions in human brain tissue, Lucchinetti et al. found two distinct pathologic patterns of remyelination: 70% of patients had both active plaques with reduced oligodendrocytes as well as remyelinated plaques with increased oligodendrocytes. The remaining 30% of patients had more extensive loss of oligodendrocytes in active lesions with virtually no evidence of

remyelination [19]. Even when repair occurs, myelin formed after inflammatory injury is qualitatively different than myelin formed during development. Study of "shadow plaques," areas of old inflammation with remyelination, shows that the myelin sheaths are thinner with shortened distances between nodes [20]. These areas are also more susceptible to a second inflammatory attack as compared with normal-appearing white matter and are more likely to suffer from progressive, long-term demyelination and axonal degeneration [21].

Strategies to enhance remyelination

Several key factors are required for successful remyelination (see Fig. 1). First, remyelination requires functionally healthy axons [22]. Studies in animal models have demonstrated that axonal release of cytokines, including neuregulin and brain-derived neurotrophic factor, enhances remyelination [23]. While oligodendrocytes can myelinate both fixed axons [6] and inert nanofibers [24, 25], neuronal activity enhances the ability of OPCs to proliferate and differentiate which in turn leads to the formation of more robust myelin [26]. As discussed above, axonal injury occurs commonly in MS and thus limits successful myelin repair.

Second, remyelination relies upon a highly regulated microenvironment with a careful balance of pro- and anti-inflammatory mediators. During acute demyelination, macrophages remove myelin debris. This process is important to remyelination as myelin debris inhibits OPC differentiation, presumably to prevent aberrant myelination during development. Through phagocytosis, the macrophages create a microenvironment which promotes remyelination [27]. Clearance of lipid debris appears to be accelerated by exercise, which may optimize the microenvironment for OPC differentiation and subsequent remyelination [28]. In addition, activated macrophages produce a host of chemokines and cytokines, including insulin-like growth factor 1, interleukin-10, and CXCL1 [29], which stimulate OPC recruitment and differentiation. This promyelination environment is counter-regulated by myelination inhibitors. One example is the wnt/beta-catenin pathway which is activated by inflammation and in turn impairs OPC differentiation [30]. Several experimental therapies modify these targets with the goal of promoting remyelination. One protein of particular interest is LINGO-1 [31], which acts through the wnt pathway and is a known inhibitor of oligodendrocyte differentiation [32].

Finally, remyelination depends upon successful differentiation and maturation of OPCs. OPCs are found throughout the adult CNS and are present in MS plaques [33, 34]. Despite this, remyelination is often insufficient. Several therapies have focused on enhancing OPC differentiation and recruitment to promote successful remyelination. Promising examples in cell culture and animal models include thyroid hormone, human monoclonal IgM antibody 22 [35], and Retinoic x Receptor gamma (RxRγ) [36] (see Fig. 1). In addition, development of in vivo [37] and in vitro [38] high-throughput screens have identified several candidate medications which promote OPC differentiation. Two notable examples,

clemastine [39••] and GSK239512 [40••], show promise as remyelination therapies and are currently being studied in clinical trials. However, it is important to understand the strengths and limitations of the available animal models of demyelination, outcome measures of myelination status, and the current framework of remyelination trial study design (as described below) when interpreting the results of these trials.

In summary, current approaches being investigated to promote remyelination include therapies that (1) block inhibitors of remyelination (e.g., anti-LINGO monoclonal antibody), (2) increase the clearance of myelin debris, (3) increase the number of OPC within the brain (e.g., transplantation of human OPC), and (4) stimulate OPC differentiation (e.g., clemastine and GSK239512). However, effective remyelination will likely require a combination of approaches in order to achieve effective remyelination. For instance, a recent study identified a synergistic interaction of exercise and clemastine; exercise improved lipid debris clearance, proliferation of OPCs, and myelin thickness, and clemastine improved OPC differentiation, resulting in remyelination of 98% of affected axons [28].

Animal models used in remyelination studies

In pre-clinical trials, animal models allow for the study of disease development and assessment of novel therapeutic approaches. However, there are important differences between animal models and MS, including phenotypic manifestations, histopathology, and disease course. These differences are important to understand when interpreting the data from these studies and their applicability to therapeutics in MS.

Lysolecithin is a white matter gliotoxin that solubilizes membranes and is selective for myelin-producing cells [41]. Remyelination begins 7–21 days after lysolecithin injection [42]. Remyelination is faster and more complete than in other CNS demyelinating models because OPCs are not affected by the toxin [43]. The advantage of this model is that the insult is localized and monophasic. However, in the lysolecithin model, there is no lymphocytic response and there are no clinical signs of demyelination [44].

Dietary supplementation with the copper chelator, *cuprizone*, causes apoptosis of oligodendrocytes and obvious demyelination 3 weeks after ingestion [45–47]. The exact mechanisms of oligodendrocyte death are not understood, but likely involve mitochondrial dysfunction and oxidative stress [48]. Acute demyelination is particularly evident in the corpus callosum and posterior cerebellar peduncles [49]. Remyelination is dependent on OPC maturation and is more apparent in white matter than gray matter [50]. Demyelination and remyelination are concurrent and occur with axonal injury, which is similar to the pattern in MS lesions [51]. Cuprizone does not cause inflammation and involvement of B and T cells, unlike MS lesions, and is not associated with any clinical signs [51, 52].

Experimental autoimmune encephalomyelitis (*EAE*) is the most commonly used animal model of MS because of its immunological and histopathological similarities to MS [53]. Active EAE induction occurs with subcutaneous administration of a myelin-related peptide and adjuvant to induce

lymphocyte-mediated demyelination and axonal degeneration with clinical paralysis [53, 54]. During the inflammatory process, dendritic cells and T cells traverse a damaged blood-brain barrier and interact with other antigen-presenting cells to amplify the inflammatory response and recruit other immune cells, leading to demyelination and axonal damage [55]. The most pronounced changes occur in the spinal cord, but the disease phenotype and histopathology vary depending on the animal species [56]. The ongoing inflammation, relapsing-remitting pattern of clinical symptoms, and involvement of B and T cells with axonal loss and demyelination are similar to what occurs with MS lesions [53]. In addition, like MS, there are clinical signs, principally paralysis [53]. However, ongoing inflammation and axonal degeneration confound the study of remyelination.

Other animal models are less commonly used to study remyelination. These include the viral model, Theiler's encephalomyelitis, and genetic models of hypomyelination and demyelination [56, 57].

Each of the animal models used to test remyelinating therapies have their strengths and weaknesses. Thus, most therapies are assessed in two or more models.

Considerations for subject inclusion and study design in clinical trials

There are many patient- and MS lesion–specific factors that may determine remyelination potential.

The rate of shadow plaque formation is highest within the first 10 years of disease onset or before approximately 55 years of age, but appears to be equally distributed between genders [58]. The decrease in remyelination with age is likely secondary to multiple factors including a reduction in OPC maturation capacity, impaired immune system, decreased myelin clearance, and epigenetic regulation [59, 60]. Shadow plaques also appear to be more prevalent in subjects with relapsing-remitting and primary progressive disease, but these differences are not statistically significant and shadow plaques are found to be present at all stages of the disease [58, 61]. Lesion location may also be important to consider as there are more shadow plaques in the supratentorial white matter than the spinal cord and optic nerve [58]. There also appears to be more remyelinated plaques in subcortical or deep white matter than in periventricular lesions [61]. Independent of location or subtype, one pathologic study demonstrated extensive remyelination in 60–96% of lesions in a small group (20%) of subjects, hinting at other undiscovered intrinsic myelinating factors [61].

Many questions also remain regarding optimal treatment conditions. Remyelination is more robust in plaques containing inflammatory cells, and OPC number is associated with the number of macrophages and microglia within a lesion [62, 63]. However, free radicals and cytokines released by immune cells can damage OPCs and mature oligodendrocytes which could destabilize early myelin formation [64]. There continues to be myelin

formation throughout the course of the lesion, but it is unclear if there is a window for optimal drug efficacy.

Measurement of remyelination in clinical trials

A significant challenge in the clinical investigation of remyelination therapies is uncertainty about the approaches to measure whether remyelination has occurred. Currently, the approaches most commonly being used include measurements of the anterior visual pathway and novel MRI techniques.

Anterior visual pathway remyelination-related outcomes

Around 50% of people with MS develop optic neuritis during the course of their disease, and many others have subclinical evidence of optic nerve damage [65, 66]. The histopathology of optic neuritis includes macrophage, monocyte, and lymphocyte infiltration with resulting demyelination and axonal injury, which is similar to MS lesions in the brain [67, 68]. Because of the frequent involvement of the optic nerves in MS and the histopathologic similarities between optic nerve damage and MS lesions within the brain and spinal cord, anterior visual pathway outcomes are commonly used in remyelination trials [69].

Damage to myelin around the optic nerve can be assessed electrophysiologically with *visual evoked potentials* (*VEPs*). VEPs are performed using scalp electrodes to measure cortical signals after a visual stimulus is introduced. After being analyzed and compared with standardized normative data, the p100 latency is calculated from the time of stimulus onset to the positive waveform deflection (about 100 ms long). A prolonged p100 latency is a reflection of impaired myelination [69]. *Multifocal VEP* is a second-generation technique that utilizes different, independent stimuli across the visual field in combination with a continuous EEG recording [70]. Multifocal VEP has better sensitivity and specificity than full-field VEP and is able to detect smaller optic nerve lesions [71]. However, both techniques can be affected by unrelated ocular disease and measurement relies on patient cooperation. Reliability of these measurements also varies depending on the electrophysiology laboratory, potentially limiting feasibility of multisite trials. VEP latencies can continue to shorten up to 2 years after an attack of optic neuritis and are abnormal in around 50% of MS patients without a clinical history of optic neuritis [72, 73]. The dynamic improvement of VEP latencies over time and ubiquitous optic nerve involvement in MS make VEPs a viable primary outcome in acute or chronic remyelination trials.

Novel imaging techniques

While conventional magnetic resonance imaging is useful to assess for new inflammatory activity in MS, it lacks the pathologic specificity necessary for remyelination trials. Therefore, novel imaging modalities and post-processing techniques are growing in popularity. *Magnetization transfer ratio* (*MTR*) measures the efficiency of proton exchange between bound macromolecules (in protein and lipid) and free protons [74]. MTR is higher in myelinated, undamaged tissue and reduced in tissue with demyelination and axonal loss [75].

As a lesion remyelinates, the MTR increases but does not return to the levels of normal-appearing white matter [76]. But notably, MTR can be influenced by axonal density, edema, and inflammation [77]. Because it can be performed on commercial scanners with short acquisition times, MTR has been widely used in clinical trials. Another ratio, *myelin water fraction* (*MWF*), measures T2 myelin water signal to total water signal [78]. This ratio was found to correlate with myelin content with limited confounding effects from inflammation and axonal density [79, 80]. However, this technique requires long acquisition times which limits its use in trials. *Diffusion tensor imaging* (*DTI*) utilizes the direction and magnitude of water molecule diffusion to assess various microstructural components [81]. Specifically, myelination status can be inferred from radial diffusivity, but can be influenced by crossing fibers, edema, and cell infiltration [82, 83]. While more pathologically specific than MTR, DTI requires longer acquisition time.

Remyelination clinical trials to date

Opicinumab

Opicinumab is an anti-LINGO1 antibody which demonstrated safety and tolerability in a phase I trial in people with MS and healthy controls [84]. As mentioned previously, the LINGO-1 protein on OPCs and neurons may negatively regulate myelination through multiple mechanisms [85]. In pre-clinical studies, LINGO1 knockout mice demonstrated increased OPC differentiation and oligodendrocyte maturation. Subsequently, an inhibitory monoclonal antibody to LINGO1 was shown to increase remyelination in EAE and lysolecithin models [86]. Anti-LINGO1 does not have detectable immunomodulatory effects [87].

The RENEW trial was a multicenter, double-blind, randomized, placebo-controlled, parallel group study of opicinumab in subjects with first unilateral onset acute optic neuritis within 28 days from symptom onset. Subjects received 1 g of methylprednisolone per day for 3–5 days prior to randomization to receive opicinumab or placebo infusions. The primary outcome was full-field p100 VEP latency after 24 weeks of therapy. Although there was no significant difference between groups in VEP latency at 24 weeks, this was achieved at 32 weeks ($p = 0.01$) [88]. Multifocal VEP was performed on a subset of patient and showed similar results to full-field VEP; post hoc analysis indicated that multifocal VEP had a larger effect size and could be suitable for future multicenter trials [89••]. The SYNERGY trial was a multicenter, double-blind, randomized, placebo-controlled, multiarm trial comparing various doses of opicinumab to interferon-beta 1a and to placebo. The trial included relapsing or secondary progressive MS subjects who were monitored over 72 weeks. Primary outcomes included the Expanded Disability Status Scale, Timed 25-Foot Walk, Nine-Hole Peg Test, and 3-Second Paced Auditory Serial Addition Test. Limited reports indicate that there was satisfactory tolerability, but failure to meet primary clinical endpoints. Peer-reviewed publication of results is anticipated.

Clemastine

Clemastine, an antihistamine, is an antagonist of H1 and reverse antagonist of M1/M3 receptors [90].

Table 1. Remyelination therapies in Phase I or ongoing Phase II and Phase IV clinical trials

Drug name	Mechanism of action	Pre-clinical data	Clinical trial stage	Outcome measures	Clinical trial identifier; status
Adrenocorticotropic hormone (ACTH)	Increases OPC number, accelerates maturation and survival. Possibly protects against effects of oxidative stress and excitotoxins [98]	Yes, glial culture [98]	Phase IV, randomized, open-label study of ACTH in RRMS and SPMS with new enhancing lesions	Primary: MWF of enhancing lesions over 12 months	NCT02446886; ongoing
Antisemaphorin 4D (VX15/2503)	Monoclonal antibody to semaphorin 4D; promotes OPC survival and differentiation [99, 100]	Yes, EAE [100]	Phase I, randomized, double-blind, placebo-controlled, dose-finding and PK study in all MS types	Primary: AE; secondary: PK	NCT01764737; completed [101]
BIIB061	Myelin protein stimulant	–	Phase I, single-arm, open-label in healthy subjects	Primary: PK; secondary: safety and tolerability	NCT02521545; Completed
Domperidone	D2/D3 dopamine receptor antagonist that activates the prolactin receptor signaling pathway. Prolactin increases OPC proliferation and numbers of myelinated axons [102]	–	a. Phase IV, single-arm, open-label, futility trial in SPMS b. Phase IV, open-label, randomized, control trial in RRMS	a. Primary: T25FW; secondary: 9HPT, SDMT, EDSS, MFIS, MSQLI b. Primary: DTI and MTI of enhancing lesions at 32 weeks; secondary: AE, serum prolactin	a. NCT02308137; ongoing b. NCT02493049; ongoing
Nanocrystalline gold	Increased differentiation of OPCs (unpublished data)	Yes, cuprizone, lysolecithin (unpublished data)	Phase II, randomized, double-blind, parallel group, placebo-controlled study in RRMS within 10 years of diagnosis (VISIONARY-MS)	Primary: mfVEP at 24 weeks; secondary: LCVA at 6 months and up to 48 weeks	NCT03536559; ongoing
Olesoxime	Cholesterol-like small-molecule compound binding to 2 compounds of the mitochondrial permeability transition pore [103]. Promotes oligodendrocyte maturation and myelin synthesis [104]	Yes, lysolecithin, cuprizone [104, 105]	Phase I, randomized, double-blind, placebo-controlled, multicenter study in patients with stable RRMS (MSREPAIR)	Primary: AE over 24 weeks; secondary: number of enhancing lesions and new or enlarging lesions over 24 weeks	NCT01808885; completed
Quetiapine	Non-selective G protein coupled receptor antagonist; stimulates proliferation and maturation of oligodendrocytes, and reduces inflammation [106]	Yes, EAE, cuprizone [106]	Phase I, multiple arm, open-label, dose escalation study in progressive MS	Primary: AE over 4 weeks	NCT02087631; ongoing

Table 1. (Continued)

Drug name	Mechanism of action	Pre-clinical data	Clinical trial stage	Outcome measures	Clinical trial identifier; status
RHIgM22	Recombinant human remyelination-promoting monoclonal IgM antibody; IgM22 binds to human oligodendrocyte surface antigens and possibly has remyelinating effects [107–110]	Yes; EAE, cuprizone [107–109]	Phase I, double-blind, placebo-controlled, multicenter, dose escalation study	*Primary:* AE; *Secondary:* PK	NCT01803867; Completed [111]
Thyroid hormone	Regulates oligodendrocyte differentiation and myelination during development [112]	Yes; EAE, cuprizone, lysolecithin [113, 114]	a. Phase I, single-arm, open-label, double-blind, randomized controlled trial in all MS types (MST3K) b. Phase I, single-arm, open-label in all MS types	a. Primary: maximum tolerated dose; secondary: reliability of VEP over 1 week b. Primary: incidence rate of AE over 26 weeks	a. NCT02760056; completed—has results b. NCT02506751; ongoing

Clinical trial data listed in the table are gathered from ClinicalTrials.gov by searching the term "remyelination" within the condition of "multiple sclerosis"; published studies are sited and unpublished data is indicated above. Search results current through January 2019. *AE*, adverse events; *DTI*, diffusion tensor imaging; *EAE*, experimental autoimmune encephalomyelitis; *EDSS*, Expanded Disability Status Scale; *LCVA*, low contrast visual acuity; *MTI*, magnetic transfer imaging; *MFIS*, Modified Fatigue Impact Scale; *mfVEP*, multifocal visual evoked potential; *MS*, multiple sclerosis; *MSQLI*, Multiple Sclerosis Quality of Life Inventory; *MWF*, myelin water fraction; *9HPT*, Nine-Hole Peg Test; *OPC*, oligodendrocyte precursor cell; *PK*, pharmacokinetics; *RRMS*, relapsing-remitting multiple sclerosis; *SPMS*, secondary progressive multiple sclerosis; *SDMT*, Symbol Digit Modalities Test; *T25FW*, timed 25-ft walk; *VEP*, visual evoked potential

Deshmukh et al. discovered the role of muscarinic antagonism in OPC differentiation. This was also confirmed using a micropillar array screen of 1000 bioactive molecules which identified a cluster of antimuscarinic drugs that enhanced remyelination. Among these antihistamines, clemastine significantly enhanced oligodendrocyte differentiation and wrapping of myelin, even when compared with known pro-remyelinating agents such as thyroid hormone [91]. In animal models, clemastine was found to improve spatial memory and increase the number of mature oligodendrocytes through its positive effects on OPC differentiation in cuprizone-treated mice [92]. In socially isolated mice, clemastine resulted in epigenetic changes in the oligodendrocytes but not in neurons of the prefrontal cortex and enhanced OPC differentiation [93].

The ReBUILD trial was a single-center, double-blind, randomized, placebo-controlled, crossover trial of clemastine in subjects with early relapsing-remitting MS with chronic optic neuropathy. Their inclusion criteria included narrow VEP and optical coherence tomography (OCT) criteria to assure both sufficient demyelinating injury (as manifested by a prolonged p100 on VEP) and persistent axons (as detected by thickness of the retinal nerve fiber layer assessed by OCT). The primary outcome was change in full-field VEP p100 latency over the 5-month trial. Using a crossover model, they detected a 1.7-ms/eye improvement in the latency delay following treatment with clemastine. However, considering the positive effect of the clemastine group into the second epoch, a delayed treatment model was also assessed. The delayed treatment model showed a 3.2-ms/eye improvement in latency delay. However, subjects experienced worsening fatigue while on clemastine [94]. Though the effects were modest, the trial helped build the foundation that a remyelination trial can be conducted over a relatively short time period in patients with chronic injury using VEP as an inclusion criterion and outcome measure.

GSK239512

GSK239512 is a selective H3 receptor antagonist with high affinity for brain H3 receptors [95]. It was initially developed using a high-throughput in vivo assay screening strategy as a treatment for Alzheimer's and schizophrenia [96–98]. A subsequent study in the cuprizone mouse model demonstrated increased OPC differentiation and enhanced remyelination [99].

Schwartzbach et al. conducted a multicenter, double-blind, randomized, placebo-controlled, parallel group study of GSK239512 in subjects with early relapsing-remitting MS with new MRI activity or relapse in the previous year. The primary outcome was the mean change in lesional MTR for new lesions that developed over the 48-week trial period. There was a small positive effect, but the trial failed to meet primary or secondary outcomes. Notably, not all subjects developed new lesions over the trial period and the trial duration was short, limiting generalizability [40••]. However, this study did show feasibility for a multicenter trial using MTR as a primary endpoint.

Discussion

Chronic demyelination in MS is a contributor to permanent impairment and progressive axonal degeneration. While there are many therapies that aim to reduce inflammation and demyelinating lesions, none are

FDA approved for remyelination. Currently, there are multiple ongoing clinical trials investigating the safety, tolerability, and efficacy of different remyelinating agents with various primary outcomes (Table 1). Likely, effective remyelination in MS will require the optimization of multiple factors, including a regulated microenvironment as well as the maturation and differentiation of OPCs. As mentioned previously, non-pharmacologic approaches, such as exercise, should be explored as potential adjunctive therapies. While high-throughput screening has increased our capacity to screen potential therapeutics, there are notable limitations of animal models to recapitulate remyelination in MS. Understanding the limitations in the pre-clinical and clinical trial data will allow for improved design in future clinical trials.

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Compliance with Ethical Standards

Conflict of Interest

Lindsey Wooliscroft and Elizabeth Silbermann each declare no potential conflicts of interest. Michelle Cameron reports consulting fees from Adamas Pharmaceuticals and Greenwich Biosciences outside the submitted work. Dennis Bourdette reports consultancy for reviewing patient medical records and providing opinion on treatments for Magellan Health Care and Best Doctors Inc. He also served as an expert witness on MS for the US Department of Justice, reports a bench research grant and collaborative center award from the National MS Society, and reports a founder's stock valued at $1000 from Llama Therapeutics.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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