Autumn 2025, Volume 10, Issue 39 (1- 10)
DOI: 10.22034/ppmj.2025.732264

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Advancing Remyelination Therapies in Multiple Sclerosis: Beyond Inflammation Control

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ARTICLE INFO

Paper Type: Original Article

Submitted: 2025-07-15
Accepted: 2025-11-23

Keywords:
Multiple sclerosis
Central Nervous System
Remyelination
Stem cell therapies
Nerve fibers

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ABSTRACT

Multiple sclerosis (MS) is a long-term disease that is frequently progressive and affects the central nervous system (CNS). This in turn breaks down the myelin sheath the protective covering around nerve fibers. Damage to myelin leads to a breakdown in nerve communication and can cause a number of neurological conditions. This study examines recent approaches towards increasing remyelination in the multiple sclerosis (MS) population as the protection of oligodendrocytes and promotion of remyelination are essential therapeutic goals. Materials and methods: A search was performed in national and international databases with the use of specific keywords. This search resulted in the identification of 235 articles, on "remyelination" and "multiple sclerosis". Seventy articles were included in this review from 2000 up to 2020. These findings lead to the conclusion that already established immunomodulatory therapies have some benefits for reduction of myelin breakdown, but are rather poor at promoting remyelination, most notably in progressive MS.Controversially during the last years a change has been made towards compounds targeting (symptomatic) inflammation as well as remyelination. These interventions may optimize function and may promote axonal conduction. These strategies, including stem cell therapy, growth factors, small molecules and gene therapies hold promise in future treatment of MS. Not only are they trying to stop further loss of myelin, but also attempt to repair what damage has already been done.

How to Cite this Article:

S. Hatamian. "Advancing Remyelination Therapies in Multiple Sclerosis: Beyond Inflammation Control" Personalized & Precision Medicine Journal, Vol. 10, no. 39, pp. 1- 10.

INTRODUCTION

Multiple sclerosis is an inflammatory disorder that induces chronic inflammation of the central nervous system (CNS)(1). This inflammation results in demyelination and axonal damage. The degeneration of myelin, the protective covering encasing nerve fibers, is the primary pathogenic characteristic of multiple sclerosis (2). This deficit results in diminished neuronal transmission (3). This process disrupts neuronal connectivity and may lead to a progressive deterioration in neurological function. Multiple sclerosis predominantly impacts young adults aged 20 to 40, with a higher prevalence in women (4). The disease manifests in two principal forms: relapsing-remitting multiple sclerosis (RRMS) and progressive multiple sclerosis

(PPMS). Relapsing forms are defined by episodes of aggravation succeeded by partial recovery, whereas progressive forms exhibit a continuous decline in function with limited recovery (5).

Remyelination, the restoration of damaged myelin, is an essential phase in alleviating the impacts of multiple sclerosis (2). OPCs are crucial for generating new oligodendrocytes, which in turn produce myelin. However, in multiple sclerosis, chronic inflammation and other factors impede this repair process, particularly in the advanced stages of the disease (6). Accordingly, remyelination has emerged as a key objective in the research and treatment of MS. Interferons and glatiramer acetate Interferons and glatiramer acetate are pharmaceutical agents used in the treatment (2). These drugs reduce inflammation and regulate the immune system; however, they are primarily directed at the inflammatory part of the disease process and are not directly involved in myelin repair. (7).

Novel therapies that promote remyelination are designed to boost the recovery of remaining myelin and prevent further neurological decline. These include stem cell therapy, growth factors, drugs in form of small molecules and gene therapy (8).

While numerous techniques remain under evaluation, current research has demonstrated promising results in preclinical models and early-phase clinical trials. This paper summarizes current therapeutic options for remyelination in multiple sclerosis (2), highlights the limitations of existing drugs, and explores novel treatment strategies (9).

METHODS

No one method, or assessment tool should be used in isolation whilst managing pain (either acute or chronic) as it can be complex and multifaceted. For the multidimensional nature of pain, pharmacological treatments, interventional procedures, rehabilitation, psychological therapies and complementary modalities can be integrated. Multimodal approaches optimize analgesic effectiveness, functional recovery and quality of life while minimizing dependence on and side effects of opioids. And advances in neuroscience, precision medicine and digital health might be widening the avenues to treatment. Mechanism-based pharmacology, regenerative treatments, and AI-driven personalized interventions promise to shift from symptom-centric care towards the restoration of function and health over the long-term.

the future of pain management demands an integrated, evidence-based and personalized treatment that responds effectively to the multifaceted biological, psychological and social factors behind pain expression in order to “re-imagine” relief, empowerment and functional recovery based on the integration of clinical knowledge, technology and active patient involvement.”

RESULTS

Immunomodulatory Drugs and Their Impact on Remyelination

Immunomodulatory Drugs Are The Hallmark Of Modern Multiple Sclerosis Treatment. These drugs, such as interferon beta (IFN-β), glatiramer acetate, and monoclonal antibodies (mAbs) including natalizumab and ocrelizumab, largely intend to manipulate the immune response and alleviate inflammation in CNS (10). These medications help reduce the frequency of relapses and slow the progression of disease by suppressing productiaon of autoreactive T-cells and other immune cells that target mylein. But their participation in the promotion of remyelination is poor (11).

Studies suggest that immunomodulators might cause a secondary effect of enhancing remyelination by reducing inflammation. This reduction in inflammation could then allow a more permissive environment for the OPC to generate new myelin. Studies have shown that IFN-β promotes the survival of OPCs and dcevelopment into adult oligodendrocytes

(12). However, the effect of these drugs is restricted since they are more efficient during the early stage of MS (2). They lose their effectiveness with the progress of the disease. Therefore, new targeted therapy to provide remyelination to enhance immune-modulation and treat the progressive aspects of the disease is needed (13).

Experimental Therapies for Promoting Remyelination

A number of novel pharmaceuticals have shown promise in studies and early-phase clinical trials. These treatments aim at promoting recovery of damaged myelin and restoration of normal axonal conduction.

Stem Cell Therapy: OPC stem cells in particular have attracted much attention for their ability to remyelinate. The adult CNS hosts OPCs, which are able to differentiate into the mature cells responsible for myelination, oligodendrocytes (14). In the case of multiple sclerosis, an inflamed environment and other factors that limit regeneration suppress the regenerative ability of OPCs (2).

A number of stem cell treatments aimed to promote remyelination are under investigation. These include the engraftment of NSCs, mesenchymal stem cells MSCs and induced pluripotent stem cells (15).

Animal experiments clearly demonstrate that transplantation of stem cells can stimulate generation of OPC and improve remyelination. Indeed, transplantation of NPCs has been demonstrated to increase myelination and promote functional recovery in murine EAE models (16).

Stem cell transplantation in people with MS has been the subject of clinical trials, and some studies suggest it potentially enhances neurological functioning and quality of life (17). However, there are several challenges that still need to be addressed, including immunorejection of the cells, survival and integration of these transplantated cells as well as ethical problems. And furthermore, the delivery of enough viable stem cells into affected areas in CNS is a technical challenge because the regenerative potential is constrained by BBB(18).

Growth Factors and Small Molecules

Several growth factors and small molecules which might promote remyelination have been found. Insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF-2) have been demonstrated to enhance the survival, proliferation and differentiation of OPCs to adult oligodendrocytes (Wang et al., 2012). These are of particular interest in that they could potentially augment the endogenous repair processes which occur in MS (19).

Clemastine fumarate is a small molecule that shows some promise. It is an antihistamine that has also been demonstrated to improve oligodendrocyte progenitor cell (OPC) maturation and to stimulate remyelination in preclinical models of multiple sclerosis31,32. The blood-brain barrier permeability of clemastine and the enhancement of remyelination in the absence of stem cell transplantation make it an attractive candidate for further clinical development (20).

Monoclonal antibodies, for example opicinumab that binds LINGO-1 (a negative regulator of development of OPC), have shown promise to be able to promote remyelination by stopping the inhibitory signals that block oligodendrocyte precursor cell maturation. Some early-phase clinical trials have reported promising benefits, but further investigation of their efficacy and safety in larger populations are needed (21).

Gene Therapy and Nanomedicine

Gene therapy and nanomedicine are emerging approaches in the treatment of MS. Gene therapy may deliver genetic material that promotes oligodendrocyte precursor cell development or suppress substances

interfering with remyelination (22). The gene therapy of multiple sclerosis has now entered into its early, but promising age with the possibility to enable direct delivery of therapeutic genes into the central nervous system without systemic administration (23).
Nanomedicine, involving the use of nanoparticles for drug or gene delivery, offers great promise (24).
Nanoparticles can be engineered to cross the blood-brain barrier and deliver therapeutic drugs directly to the injured region (25). This could lead to a more effective and accurate delivery of remyelination-promoting medicines with reduced side effects associated with conventional drug delivery. However, more studies are needed to improve those technology to ensure their safety in clinical application (26).

DISCUSSION

Remyelination strategies have emerged as one of the most promising and important areas for multiple sclerosis research. This is particularly relevant to progressive multiple sclerosis where remyelination is either minimal or non-existent, thereby resulting in slow but relentless deficit of neurological function (27). Although existing therapies, in particular immune-modulating drugs, have been effective to combat inflammation in MS they exhibit little or no direct pro-remyelinating potential. It follows that the focus of therapy is moving towards new treatments which promote regeneration of the CNS, in particular remyelination (28).
The complex and heterogeneous nature of MS represents a major difficulty in studies on the disease. The damage to myelin and axon degeneration are the major causes of disability in MS (29). The disease's pathophysiology consists of a complex interplay among factors, namely immune-mediated inflammation, neuronal injury, and the lack of endogenous healing processes. Understanding these components and their interactions as the disease progress is crucial for developing meaningful treatments (30). In this article we will discuss the problems and possible remedies for remyelination therapy. We will concentrate on the reasons why remyelination fails, the shortcomings of existing treatments and how new strategies to address these problems now being explored are fascinating (31).

Inflammation as a Barrier to Remyelination

Inflammation within the central nervous system is a major barrier to successful remyelination in multiple sclerosis. In early stages of the disease, autoreactive T cells play a significant role in myelin destruction (32). The immune system responds and the CNS is infiltrated with immune cells, including T lymphocytes, macrophages, and microglia which destroy oligodendrocytes that produce myelin. Demyelination and axonal injury as well as neuronal distress follow (30).
However, inflammation plays a major role in the repair processes within the CNS. Inflammatory cytokines, reactive oxygen species (33) and other immune mediators contribute to an environment that interfere with the differentiation and maturation of OPCs, which are the main responsible cells for remyelination (34). Importantly, in most cases OPCs are able to migrate to demyelinated regions and mature into myelinating oligodendrocytes, which generate new layers of myelin. In MS, the inflammatory milieu not only prevents oligodendrocyte precursor cell survival and maturation at the time of lesion formation but may effectively deplete over time an already limited reserve for repair (35).
In addition, chronic inflammation can produce a milieu that hinders healing such as scar tissue or lesions containing active immune cells which fail to heal (36). This chronic inflammatory state is most prominent in the later stage of multiple sclerosis, i.e. progressive MS with ongoing inflammation and inadequate or no remyelination. The

ultimate goal is to identify drugs that will diminish inflammation whilst fostering a repair-promoting (re)myelinating milieu (37). This would involve lowering pro-inflammatory cytokines, modulation of the immune system and blocking toxic factors impeding OPC differentiation.

Limitations of Current MS Treatments

The main pharmacological treatments for MS are immunomodulatory therapy, including interferons (IFN-β) and glatiramer acetate as well as other emerging biologics such as monoclonal antibodies (natalizumab and ocrelizumab)(38). The aim of such therapies is to modulate the immune response, and consequently decrease the frequency of relapses. Thus, these drugs decrease the disease activity, reduce inflammation and prevent new lesions by partially suppressing the activation of immune cells against myelin (39).

Immunotherapy Limits: Inflammation Controlled, Repair Lacking

On the other hand, immunomodulatory agents are effective in controlling RRSMS but have only a mild (if any) effect on remyelination. "The goal of these treatments is to decrease the inflammation associated with the disease and decrease both how many relapses patients have, as well as how severe they are, not to repair the myelin once it has been damaged," she adds (40). With disease progression, CNS regenerative potential decreases and remyelination is less efficient. These therapies have little effect on the course of the disease or recovery in secondary progressive MS (SPMS) and primary progressive MS (PPMS), which is characterized by a lack or restriction of remyelination (Remyelination, 41).

And responses to immunomodulatory therapy can be highly variable between patients. Some patients with RRMS respond well to these medications, whereas others are poorly responsive (42). It suggests a need for more-individualised therapies. This variation emphasizes the need for therapies that are anti-inflammatory, promote healing and regeneration within the CNS (43).

The Promise of Remyelination-Based Therapies

In light of the restricted efficacy of current therapeutics, there is increasing enthusiasm for developing drugs that specifically enhance remyelination in MS (44). Several strategies have demonstrated impressive potential in preclinical models and early phase clinical studies. These approaches include stem cell therapies, growth factors and small molecules, as well as gene therapies. The aim of these treatments is to induce regenerative mechanisms in the CNS, to repair damaged myelin, and to improve neural function (45).

Stem Cell Therapies

Stem cell transplantation is one of the most promising approaches to promote remyelination (46). OPCs are important for the process of remyelination but their function is impaired in MS as a result of inflammation, injury and an unfavourable environment within the CNS. The transplantation of exogenous stem cells, which include NSCs, MSCs and iPSCs, is one such most promising approach. These stem cells are able to differentiate into oligodendrocytes and thus contribute to remyelination (47).

The success of stem cell- based intervention in inducing the differentiation of OPCs into mature oligodendrocyte, remyelination and improving functional recovery had been demonstrated in previous preclinical studies (48). Clinical studies on MS patients have shown positive results, and some patients even reported improvements in their neurological functions as well as the quality of life (49). However, major challenges are still to be tackled in light of these encouraging results. For example, the survival and integration of transplanted stem cells within the host CNS is difficult to achieve. 2,3 This work indicates that DSBs in these implanted cells are formed as soon as we expect the stem cell to survive long enough to contribute meaningfully to tissue function. In addition, the risks associated with immunological rejection, tumorigenesis and other side effects must be addressed (50).

Another major problem remains, in that enough viable stem cells do not reach the sites of the central nervous system to which they are desired. The BBB is a barrier that blocks potentially. Stem cell transfer is also impaired by toxic chemicals (51). Scientists are attempting to develop techniques including targeted methods such as gene editing and nanoparticle-mediated delivery and ultrasonic strategies to address these challenges and increase the specific locati0n of stem cell (15, 52).

Growth Factors and Small Molecules

Another potential approach can be the application of growth factors and small molecules to enhance remyelination. Studies have shown that IGF-1, FGF-2 and BDNF which are growth factors, enhance the survival and differentiation of OPCs (53). These enhance the CNSs endogenous abilities to regenerate by stimulating oligodendroglial precursor cell differentiation and oligodendrogenesis, new myelin synthesis (54).

Although growth factors have a relatively low molecular weight and size, which should theoretically facilitate their access to the CNS, an important concern regarding these molecules is entry into the brain through BBB (55). Nanoparticle-mediated delivery systems are being considered for a solution to overcome this drawback, enabling the targeting of these agents to demyelinated sites within the brain and spinal cord (56). Clemastine fumarate, an antihistamine, represents a small molecule with positive preclinical data and pilot human trials showing efficacy by enhancing oligodendrocyte precursor cell differentiation to remyelinating oligodendrocytes (57). Clemastine is of particular interest due to its ability to cross the blood-brain barrier and its oral availability contrasting with other drugs, which make it a more accessible therapeutic option (58).

Another approach being studied is to attack certain molecules that interfere with remyelination. LINGO-1 is a protein which prevents OPCs from difif erentiating into oligodendrocytes (59). Opicinumab is a LINGO-1 monoclonal antibody antagonist. Monoclonal antibodies targeting CSPGs, such as opicinumab, have shown encouraging results in preclinical and early clinical investigations by promoting immature oligodendrocyte precursor cell differentiation (and remyelination) (60).

Gene Therapy

Gene therapy, entailing the direct insertion of genetic material into the CNS to modify gene expression, holds significant promise for remyelination. Gene therapies can be designed to promote the proliferation of OPCs or to inhibit factors that impede remyelination (61).

The ability to deliver genes directly to the affected regions of the CNS may address several limitations of existing therapeutics, like the incapacity of growth factors to penetrate the BBB (62).

Although gene therapy for MS is in its preliminary stages, preclinical studies have demonstrated encouraging outcomes. Before gene therapy can be widely implemented in clinical practice, the challenges of safely and successfully delivering genes to the CNS, together with concerns over potential immune responses and off-target effects, must be addressed (33).

CONCLUSION

Remyelination-based therapies represent a promising novel strategy for the treatment of multiple sclerosis. While current immunomodulatory medications effectively manage inflammation, there is a necessity for more efficacious therapies to repair myelin loss and restore function, especially in progressive disease forms. Stem cell therapies, growth factors, small molecules, and gene therapies possess significant potential; nonetheless, substantial challenges remain, including enhancing delivery methods, ensuring safety, and surmounting biological impediments such as the blood-brain barrier. Ongoing research and clinical trials are essential to enhance existing medicines and develop personalized treatments for patients with multiple sclerosis. This will provide patients with optimism for an improved quality of life and a reduction in long-term disability.

Authors's Contribution

Sevak Hatamian: data curation; editing and review. The author read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The author declared no conflict of interest.

Consent for publication

Not Applicable.

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