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Neuroprotective Strategies for Multiple Sclerosis: Advancing Therapeutic Approaches to Preserve Neuronal Function and Promote Repair

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation and demyelination, leading to substantial disability and socioeconomic burden. With the absence of a definitive cure for MS, there is a critical need to explore neuroprotective strategies that can preserve neuronal function and impede disease progression. This article provides a comprehensive review of current knowledge and emerging therapeutic approaches to preserve neuronal function and promote repair in individuals with MS. The review highlights neuroprotective strategies, including immunomodulatory therapies, neuroreparative agents, and lifestyle modifications, that have shown promise in clinical studies. Additionally, the article discusses the potential of personalized treatment approaches based on individual MS profiles and the use of emerging neuroregenerative therapies to improve patients' quality of life and prevent relapses. By enhancing our understanding of these neuroprotective strategies, it is hoped that more effective management of MS can be achieved, reducing the disease's impact on patient's lives.

Keywords: Multiple Sclerosis; Neuroregeneration; Neuroprotective strategies; Disease-Modifying Treatment; Relapsing Multiple Sclerosis; Remyelinating therapies

Abbreviations: MS: Multiple Sclerosis; RR: Relapsing/Remitting; SPMS: Secondary-Progressive Multiple Sclerosis; FDA: The Food and Drug Administration; PML: Progressive Multifocal Leukoencephalopathy; BDNF: Brain-Derived Neurotrophic Factor; CNTF: Ciliary Neurotrophic Factor; NGF: Nerve Growth Factor; GDNF: Glial Cell Line-Derived Neurotrophic Factor; FTY720: Fingolimod; S1P: Sphingosine-1-Phosphate; JCV: JC virus; CNS: Central Nervous System; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; PUFA: Polyunsaturated Fatty Acid; PL: Poly-L-Lysine; EDSS: Expanded Disability Status Scale; RXR: Retinoid X Receptor; OPC: Oligodendrocyte Precursor Cell; ESCs: Embryonic Stem Cells; HSCs: Hematopoietic Stem Cells, NSCs: Neural Stem Cells; MSCs: Mesenchymal Stem Cells; iPSCs: Induced Pluripotent Stem Cells; IDO: Indoleamine 2,3-dioxygenase; SVZ: Subventricular Zone; DG: Dentate Gyrus

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by inflammation and damage to the myelin sheath, the protective covering of nerve fibers. This damage disrupts the normal flow of electrical impulses along the nerves, leading to a wide range of neurological

symptoms, including fatigue, difficulty with coordination and balance, muscle weakness, and cognitive impairments [1]. Epidemiologically, MS affects individuals worldwide, with varying prevalence rates across different regions. The prevalence of MS is estimated to be around 0.1% to 0.15% globally, meaning that approximately 1 to 1.5 million people are affected. Incidence rates of MS, representing the number of new cases per year, range from 2 to 10 per 100,000 individuals. Mortality rates in MS are generally lower compared to the general population, with estimates indicating a slightly increased mortality risk by around 2% to 3% compared to unaffected individuals [1-3].

The exact cause of MS remains unclear, but it is believed to involve a combination of genetic and environmental factors. Several risk factors have been identified, including a family history of MS, certain viral infections like the Epstein-Barr virus, and environmental factors like low vitamin D levels and smoking [2,3]. The physiopathology of MS involves an abnormal immune response in which the body's immune system mistakenly attacks the myelin sheath, leading to inflammation and subsequent damage to the nerves. This immune-mediated process forms scar tissue (sclerosis) within the affected areas of the central nervous system, further disrupting the normal functioning of the nerves [3].

The clinical presentation of MS can vary widely among individuals and depends on the location and extent of nerve damage. Common symptoms include fatigue, numbness or tingling, muscle weakness, problems with coordination and balance, visual disturbances, and cognitive impairments. The symptoms may come and go or worsen over time, leading to significant disability in some cases. MS diagnosis involves clinical evaluation, medical history, neurological examination, and diagnostic tests [1,4]. These tests may include magnetic resonance imaging (MRI) to detect areas of inflammation and damage in the central nervous system, cerebrospinal fluid analysis to look for specific markers, and evoked potential tests to assess nerve function. Treatment for MS aims to manage symptoms, slow disease progression, and improve quality of life. This typically involves a multidisciplinary approach that includes medications to reduce inflammation and modulate the immune system, symptom management strategies such as physical and occupational therapy, and lifestyle modifications [2,5]. Disease-modifying therapies, such as immunomodulators and monoclonal antibodies, may be prescribed to modify the course of the disease and reduce relapse rates. This article aims to provide a comprehensive overview of neuroprotective strategies for multiple sclerosis, focusing on advancing therapeutic approaches to preserve neuronal function and promote repair to improve outcomes for individuals living with this challenging disease.

Anti-inflammatory and immunomodulatory agents

Currently, there is no definite cure for MS. However, immunomodulating and anti-inflammatory agents can diminish its progression and decrease some pathological symptoms. Immunomodulating agents, including interferon beta and glatiramer acetate, are used in nonsymptomatic MS, relapsing-remitting MS (RRMS), and secondary-progressive multiple sclerosis (SPMS). These agents can reduce some of the MS symptoms by inhibiting immune cell activation, a decrease of proinflammatory cytokines production, matrix metalloproteinase activity reduction, induction of anti-inflammatory cytokine secretion, and increasing expression of Foxp3 in CD4+ and CD25+Treg cells [6]. The Food and Drug Administration (FDA) 2010 approved fingolimod as a treatment aimed at reducing the frequency of clinical exacerbations and delaying the progression of physical disability in patients with relapsing forms of multiple sclerosis [7]. Fingolimod (FTY720) is an orally available sphingosine-1-phosphate (S1P) receptor modulator with unique and potent immunoregulatory properties. Mechanistic studies indicate that on phosphorylation, fingolimod can bind with high affinity to S1P1 receptors [8]. There are at least 5 S1P receptor subtypes, known as S1P subtypes 1-5 (S1P1-5), 4 of which bind fingolimod-phosphate. These receptors are expressed on a wide range of cells involved in many biological processes relevant to MS. S1P1 plays a crucial role in the immune system, regulating lymphocyte egress from lymphoid tissues into circulation [8,9]. Studies suggest that fingolimod may also directly affect the central nervous system since sphingolipids and S1P receptors are expressed on oligodendrocytes, astrocytes, microglial cells, and neurons. The risks of adverse effects with fingolimod remain uncertain, especially in the long term. The risks include severe infections, such as disseminated and central nervous system herpetic infection; effects on immune surveillance (a possible increase in the risk of progressive multifocal leukoencephalopathy, toxoplasmosis, or neoplasms); and effects on the reproductive system after long-term use [7-9]. Fingolimod benefits relapse rates in patients who discontinued natalizumab before the study, suggesting that fingolimod provides disease control after natalizumab discontinuation [7,10].

Natalizumab is an α4 integrin antagonist that has been demonstrated to reduce disease activity and improve disease severity in patients with RRMS [7,9]. Its use, however, can be associated with progressive multifocal leukoencephalopathy (PML), an uncommon but severe and potentially fatal opportunistic brain infection caused by the JC virus (JCV), which most likely results from compromised brain immunosurveillance [7,11]. The PML risk in a pooled clinical trial cohort has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months [7,10]. Therefore, in patients found to be anti-JCV seropositive, a switch from natalizumab to another treatment is considered in order to mitigate the increased risk of PML. Other factors may also lead to a decision to discontinue natalizumab, for example, persistent anti-natalizumab antibodies, suboptimal efficacy, tolerability issues, or patient preference for oral therapy. However, natalizumab discontinuation could rapidly return

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relapse activity and MRI lesion development to pretreatment levels [7,11]. At present, natalizumab should be suggested only for patients who meet the criteria of recent inflammatory disease activity (one or more relapses within the past year, with or without the presence of gadolinium-enhancing lesions on MRI and documented evidence that alternative medications have been ineffective or poorly tolerated [12]. Patients beginning treatment with natalizumab should have taken no immunosuppressive medications in the preceding 3 months, they should have no condition that compromises cell-mediated immunity (including coexisting rheumatologic or hematologic disorders), and their leukocyte counts, at minimum, should be average [7-9].

Neurotrophic factors

Neurotrophic factors play a crucial role in neurons' development, maintenance, and survival and have emerged as potential therapeutic targets for MS. Among the neurotrophic factors implicated in MS, brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) have garnered significant attention [13,14]. BDNF, a member of the neurotrophin family, is widely distributed in the CNS and acts on various neuronal populations. It promotes neuronal survival, differentiation, and synaptic plasticity. In MS, BDNF exerts neuroprotective effects by preventing demyelination, reducing neuronal damage, and promoting remyelination. Studies have shown that BDNF levels are reduced in MS patients, suggesting its involvement in disease pathogenesis. Enhancing BDNF signaling has been explored as a potential therapeutic strategy for MS, and preclinical studies using BDNF gene therapy or BDNF mimetics have shown promising results in promoting myelin repair and improving disease outcomes [14,15]. The preliminary results of a systematic review with 689 patients with MS and 583 controls indicated that MS patients had statistically significantly lower levels of BDNF than controls [16]. CNTF, a member of the interleukin-6 cytokine family, is primarily produced by astrocytes and acts on multiple cell types within the CNS. CNTF exerts neuroprotective effects by promoting the survival and differentiation of oligodendrocytes. In experimental models of MS, CNTF administration has demonstrated beneficial effects on remyelination and functional recovery. However, the clinical translation of CNTF-based therapies has been challenging due to the limited ability of CNTF to penetrate the blood-brain barrier and the need for invasive delivery methods [13-15].

In addition to BDNF and CNTF, other neurotrophic factors such as nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) have also been investigated in the context of MS. NGF promotes neuronal survival and axonal regeneration. At the same time, GDNF supports the survival and function of dopaminergic neurons. These factors may have potential therapeutic applications in MS, but further research is needed to fully understand their mechanisms of action and evaluate their efficacy in clinical settings [17]. One study measured the levels of the mRNAs encoding these neurotrophic molecules and their related receptors in the control group and the MS cortex by RT-PCR. Except for the BDNF receptor, which was increased in the MS cortex by 2.4-fold, all other neurotrophic factors and receptors were similar in the control and MS cortex. These results raise the possibility that activation of CNTF signaling is the main neuroprotective pathway induced in the cortex as an endogenous response [18].

Neurotrophic factors hold great promise for preventing and treating MS by promoting neuronal survival, protecting against demyelination, and facilitating remyelination. Modulating the expression or activity of these factors may help mitigate the neurodegenerative processes underlying MS and improve clinical outcomes for patients. However, it is essential to note that the development of effective neurotrophic factor-based therapies for MS faces several challenges, including the need for targeted delivery methods, optimization of dosing regimens, and overcoming potential side effects. Further research and clinical trials are necessary to determine the safety and efficacy of neurotrophic factor-based interventions in MS [15-19].

Antioxidants

Multiple studies have investigated the contribution of oxidative/nitroxidative stress to the cause, progression, and clinical symptoms of multiple sclerosis. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play an essential role in the pathology of the disease, primarily when a disparity occurs, either from an increased generation or suboptimal antioxidant protection. Oxidative stress contributes to mitochondrial dysfunction, which, in turn, has been proven to lead to neurodegeneration. Protein, lipids, and DNA oxidation give rise to demyelination and glial cell and neuron damage; oxidative stress contributes to neuroinflammation, creating more oxidative stress [20]. These findings have led to active research on antioxidants' role in MS. Antioxidants are important for myelin integrity, inhibiting the oxidation of essential fatty acids by free radicals in membrane phospholipids [20,21]. Different endogenous antioxidants have been studied to understand their effects on MS. Among these, glutathione reductase, which catalyzes the production of reduced glutathione (GSH), is used to reduce ROS and is diminished in patients with MS. Superoxide dismutase catalyzes the formation of hydrogen peroxide, a less injurious free radical, and is used as a potential marker of oxidative stress intensity in neuroinflammation [21]. Antioxidant-rich diets that include low-fat dairy products, vegetable oil, onion, whole grain, soy, refined grains, organ meats, coffee, legumes, and vegetarian and lacto-vegetarian diets have been proven to reduce MS risk. In contrast, a diet high in animal fat is related to a higher prevalence of MS. The Mediterranean diet, which is antioxidant-rich, reduces the risk of multiple sclerosis [20].

In numerous studies, Polyunsaturated fatty acid (PUFA) supplementation, such as oleic acid, linoleic acid (n-6), and azelaic acid, led to a reduction of T-cell proliferation in patients with MS,

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as well as mitigation in levels of proinflammatory cytokines like IL-2, TNF, and IFN-γ [21,22]. A 24-month driven longitudinal research, which studied the effect of a mixture supplement containing omega-3 and omega-6 PUFAs, vitamin A, vitamin E, and γ-tocopherol on gait and functional capacity parameters on patients with MS, explicitly relapsing-remitting MS (RRMS), showed noticeable results, with improvement in spatiotemporal parameters such as support, step and stride time as well as gait quality. Various functional capacity tests, such as sit-to-stand tests, also showed improvement, supporting their protective role against the functional deterioration of patients with MS. However, the small sample size was a limitation, indicating an opportunity to conduct further studies with a more significant population [20,22]. GEMSP, a therapeutic compound that consists of a mixture of functional polypeptides that includes fatty acids, antioxidants, free radical scavengers, and amino acids linked individually to poly-L-Lysine (PL), is rising as a promising drug for MS treatment. Pre-clinical studies performed in animals showed that GEMSP helps to preserve myelin integrity, inhibits brain leukocyte infiltration, and eliminates autoimmune encephalomyelitis, the primary animal model used to study MS. Clinical trials reported a stable Expanded Disability Status Scale value, with a proportion of patients decreasing its value versus an expected progression on the mean EDSS scale [21].

Remyelination-promoting therapies

Remyelination, the process of restoring the damaged myelin sheath in the central nervous system (CNS), is a critical therapeutic target in MS. Several remyelination-promoting therapies have been investigated, each with its mechanisms and potential benefits for the prevention and treatment of MS. Agonists of the retinoid X receptor (RXR) have emerged as promising candidates for remyelination. RXR is a nuclear receptor that regulates gene expression and plays a crucial role in oligodendrocyte differentiation and myelin formation [23,24]. Experimental studies have shown that RXR agonists, such as bexarotene and acitretin, can promote oligodendrocyte maturation and enhance remyelination in animal models of MS. These agonists exert their effects by activating RXR-mediated signaling pathways, which stimulate the production and maturation of oligodendrocytes, leading to the repair of myelin damage. Clinical trials investigating RXR agonists for remyelination in MS are currently underway and hold great potential for improving disease outcomes [24,25].

Small molecules that enhance oligodendrocyte precursor cell (OPC) recruitment and differentiation have also garnered significant interest. OPCs are the progenitor cells capable of differentiating into mature oligodendrocytes, which produce myelin. Various compounds, including benztropine, clemastine, and sobetirome, have been investigated for their ability to stimulate OPC proliferation, migration, and differentiation. These molecules act on specific cellular receptors and signaling pathways, promoting the recruitment and maturation of OPCs, and ultimately facilitating remyelination. Early clinical trials exploring these small molecules have shown promising results in enhancing remyelination and improving functional outcomes in MS patients [26,27]. Other approaches, such as stem cell therapies and biologics targeting specific molecules involved in remyelination, are also being investigated. Stem cell transplantation can potentially replenish the damaged oligodendrocyte population and promote remyelination. Various types of stem cells, including mesenchymal stem cells and neural precursor cells, have shown promise in preclinical and early clinical studies. Biologics, such as anti-LINGO-1 antibodies, aim to block inhibitory molecules that limit remyelination and promote axonal repair in MS. These remyelination-promoting therapies are of utmost importance in preventing and treating MS. Restoring proper myelination can protect and preserve nerve fibers, prevent axonal damage, and improve overall neurological function [24-27]. By promoting remyelination, these therapies have the potential to slow disease progression, reduce disability, and enhance patients' quality of life. However, further research and clinical trials are necessary to fully understand these therapies' safety, efficacy, and long-term effects on MS.

In a recent randomized prospective study conducted by Brown et al. [28] patients with RRMS were recruited from two centers in the UK. The study included a total of 52 participants, who were assigned to receive either bexarotene (n=26) or placebo (n=26). The researchers investigated the adverse events experienced by the participants in each group. The results showed that participants who received bexarotene had a higher mean number of adverse events than those who received the placebo. Specifically, the mean number of adverse events in the bexarotene group was 6.12, with a total of 159 events reported. In contrast, the placebo group had a mean number of adverse events of 1.63, with a total of 39 events reported. All participants who received bexarotene experienced at least one adverse event. The most commonly reported adverse events in the bexarotene group included central hypothyroidism (n=26, compared to none in the placebo group), hypertriglyceridemia (n=24, compared to none in the placebo group), rash (n=13, compared to one in the placebo group), and neutropenia (n=10, compared to none in the placebo group). Based on these findings, the researchers concluded that using bexarotene to treat patients with MS is not recommended due to its poor tolerability and negative primary efficacy outcome. However, they noted that some exploratory MRI and electrophysiological analyses did show statistically significant effects, suggesting that other retinoid X receptor agonists could be further investigated for their potential minor biological effects in future studies [28].

Neuroregenerative therapies

Regenerative medicine is one of the fields of medicine that focuses on functional repair or regeneration of cells, tissues, and even organs. This reparative technology is promising,

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especially regarding neurological diseases [29,30]. In MS, the inflammatory process in the CNS leads to demyelination. The affected demyelinated regions can undergo partial remyelination, leading to structural repair and recovery of function. Attempts to regenerate myelin can be recognized pathologically in the brains of MS patients by the existence of shadow plaques, which are partially remyelinated lesions. Analysis of brain tissue from MS patients suggests several different pathological patterns of demyelination [30-32].

Stem cell therapy involves administering stem cells into the damaged brain or nervous system so that these cells differentiate into neural cells and repair the damaged tissue. Growth factor therapy involves the administration of molecules that stimulate the growth and differentiation of brain and nervous system cells. Recent research advances in regenerative therapies for neurological diseases have resulted in a great deal of research in the field of regenerative medicine [29,30]. Stem cells are unspecialized cells in the body that retains the ability to generate cells of an undifferentiated state identical to themselves or differentiate into other types of body cells with specialized functions. There are various types of stem cells, such as embryonic stem cells (ESCs), hematopoietic stem cells (HSCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs). Stem cell therapies may serve as a potential therapy for neurodegenerative disease. Among the various types of stem cells, the efficacy and safety of MSCs have long been well-established and characterized. However, the recent advancements in iPSCs make them a promising candidate for autologous therapy. MSCs and iPSCs can be obtained from patients relatively easily and expanded for use [31-32].

Mesenchymal Stem Cells (MSCs) are non-hematopoietic adult stem cells with self-renewal ability, originating from the mesoderm, but possess a multilineage differentiation capacity. Certainly, MSCs can differentiate not only toward mesoderm lineages, such as chondrocytes, osteocytes, and adipocytes, but also toward ectodermic and endodermic cells [32]. MSCs were first isolated from the bone marrow but are also found in adipose tissue, umbilical cord, dental tissues, birth-derived tissues, and others. It has been recently reported that MSCs are able to differentiate into non-mesenchymal cell lineages, such as skeletal myocytes, neurons, and cells of the visceral mesoderm, both *in vitro* and *in vivo*. Much research has focused on exploiting the pleiotropic properties of MSCs as a basis for cell therapy for a variety of neurodegenerative disorders, including MS. The immunomodulatory, immunosuppressive, neurotrophic, and repair-promoting properties of MSCs make them an attractive candidate for MS. Paracrine signals predominantly mediate the effects of MSCs on immunomodulation and remyelination, and several secreted soluble molecules, TGF-β1, IFN-γ, indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2, have been identified as significant contributors to these beneficial effects [30,31].

Takahashi and Yamanaka's groundbreaking research led to the generation of induced pluripotent stem cells (iPSCs), which are currently being used successfully to generate different neuronal cell types which can produce fully functional cells [33]. Specific patient iPSC-derived cells can recapitulate many pathological disease features at the molecular level, thus offering a unique platform to model and study many aspects of neurodegenerative disease. The recent improvements in generating autologous iPSCs from almost any somatic cell type have brought autologous cell therapies to the forefront of clinical research [30,31]. Stem cell therapy using MSCs or iPSCs shows excellent potential as a treatment for MS. However, many issues and limitations need to be resolved. The specific cell stage to be transplanted, proper characterization of the cell type to be administered, *in vivo* fate of transplanted cells in different inflammatory models, dose, route of administration, duration of therapeutic effect, and genomic stability of stem cells need further exploration and quantification. Patient-derived iPSCs also represent a novel tool in modeling MS pathology enabling the confirmation of positive responders to new pharmacotherapy and implementation of patient-specific therapeutic management [31,32]. Additionally, in the last decade, growing interest has focused on utilizing neural stem cells (NSCs) to promote remyelination. In the adult CNS, tissue-specific germinal niches, such as the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus (DG) of the hippocampus, contain multipotent NSCs with the capacity to self-renew and differentiate into functional neurons and glia [34].

In view of the multiple mechanisms by which neural precursor cells may induce beneficial effects in MS, including their regenerative potential and their trophic, immunomodulatory, and neuroprotective properties, they seem to be an excellent candidate for cell therapy. Specifically, they may have an advantage on committed myelin-forming cells that might not possess other stem cell properties and on non-neural cells that cannot perform remyelination. However, as previously discussed, these hypotheses need to be examined in clinically relevant models. In addition, the value of transplanting purified cell populations *versus* a mixture of stem cells and OPCs need to be directly compared [35].

Conclusion

This narrative review article has explored various neuroprotective strategies for multiple sclerosis (MS), shedding light on potential therapeutic interventions to preserve neuronal function and limit disease progression. The findings demonstrate the complexity of MS pathogenesis and the importance of targeting neuroprotective mechanisms to achieve optimal patient outcomes. The reviewed studies have highlighted the significance of immunomodulatory and neuroregenerative approaches in managing MS. Strategies targeting the immune system, such as disease-modifying therapies and immunomodulators, have shown promising results in reducing inflammation and preventing

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relapses. Additionally, neuroregenerative strategies, including remyelination and neurotrophic factor therapies, hold great potential for promoting neuronal repair and enhancing functional recovery, quality of life, and overall well-being of individuals with MS.

Despite the advancements in understanding the neuroprotective strategies for MS, several challenges and unanswered questions remain. The heterogeneity of the disease, varying clinical phenotypes, and the dynamic nature of MS progression necessitates further research to optimize treatment approaches. Further large-scale prospective research studies are crucial to satisfactorily elucidate the underlying mechanisms of neuroprotection, identify novel therapeutic targets, evaluate the long-term efficacy and safety of emerging treatments, and improve patient outcomes.

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