REVIEW

Clinical neurorestorative progress in multiple sclerosis

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Abstract: With the chronic progress of the disease, the majority of patients with multiple sclerosis will eventually become severely disabled and unable to live independently. Neurorestorative strategies, including cell therapy and neuromodulation, combined with neurorehabilitation, have shown encouraging signs that may benefit multiple sclerosis patients. This review indicates current progress in this area.

Keywords: demyelinating disease, immunosuppression, cell therapy, neuromodulation, neurorehabilitation

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS). Typical MS starts between 20 and 40 years of age, and women are affected approximately twice as often as men.[1] The pathological changes of the CNS in MS involve invasion by inflammatory cells, demyelination, deposition of immunoglobulin and complement, gliosis, remyelination, and axonal loss.[2,3]

Patients with MS suffer from transmission functions of the CNS due to tissue damage, which are manifested by a wide range of neurological symptoms, such as numbness, motor weakness, visual impairment, diplopia, ataxia, fatigue, urinary urgency or retention, pain, depression, and cognitive dysfunction, among others. Clinical manifestations vary among patients, as well as in different phases of the disease in each patient.[4]

Intravenous high-dose steroids have become the standard for treating an acute relapse of MS to reduce inflammatory damage to the myelin sheath and axon and hasten recovery from inflammation.[5] Plasma exchange by removing the immunoinflammatory substances can improve clinical manifestation in patients who are unresponsive to steroids.

Immunomodulatory agents, also called disease-modifying drugs, such as IFNβ, glatiramer acetate, and fingolimod, are currently considered first-line therapies for relapsing–remitting MS.[6] Symptomatic management is an important part of care of patients. Baclofen, tizanidine, and gabapentin may reduce spasticity.[7,8] Oral oxybutynin[9] and injection of botulinum toxin A[10] can effectively reduce bladder overactivity to improve bladder symptoms. Carbamazepine,[11] lamotrigine, gabapentin,[12] or oxcarbazepine[13] can benefit paroxysmal pain in MS patients. Treatment with amantadine or modafinil can improve fatigue in patients with relapsing–remitting MS.[14] Donepezil improved learning and memory in MS patients with cognitive impairment in one clinical

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trial,[15] but was not superior to placebo in another clinical trial for improving MS-related cognitive dysfunction.[16] These conventional treatment strategies can reduce inflammatory reaction and improve clinical symptoms, but do not halt neurodegeneration (Table 1). Recently, neurorestorative strategies have shown the potential to extend results beyond conventional treatment, and are briefly summarized in this review.

Cell therapies

Hematopoietic stem cells

In an initial small clinical trial, patients with MS who received hematopoietic stem cells (HSCs) showed a stable or improved Expanded Disability Status Scale (EDSS) score without new lesions on magnetic resonance imaging (MRI).[17] HSC therapy in subsequent trials has been associated with sustained clinical improvement.[18–22] Maintenance treatment was not needed in the absence of disease progression. However, patients who experienced neurological relapse and deterioration after cell transplantation needed further immunosuppression treatment.[23] More than 600 cases of HSC transplantation have been reported worldwide in the medical literature since 1995.[24] Patients with severe, highly active forms of progressive MS unresponsive to conventional treatments experienced a high rate of sustained remissions following HSC transplantation,[25] although some patients developed infections, CNS toxicity, and even mortality.[24]

Mesenchymal stromal cells

Bone marrow mesenchymal stromal cells

The mean EDSS score in MS patients after transplantation of autologous bone marrow mesenchymal stromal cells (B-MSCs) improved in one study.[26] In another study, visual acuity and visual evoked response latency in patients with secondary progressive MS also improved, with an increase in optic nerve area.[27] Patients in a small trial showed visual improvement, but without arrest of progression of lesions on MRI after B-MSC transplantation.[28] Patients in another pilot study also failed to show treatment effects on EDSS score or MRI assessment.[29] The limited therapeutic efficacy after B-MSC transplantation may be related to the absence of immunosuppressive preconditioning.

Umbilical cord mesenchymal stromal cells

The course of patients with refractory progressive MS became stable after receiving transplantation of umbilical cord MSCs (U-MSCs).[30,31] The treatments were tolerated well without significant adverse events.[31]

Olfactory ensheathing cells

The symptoms and signs of patients with MS have been shown to improve for several months with transplantation of olfactory ensheathing cells.[32,33]

Mechanisms of cell therapies

Preclinical animal studies indicate that functional recovery after cell transplantation does not correlate with the amount of neural cells originating from transplanted cells or replacing damaged cells, and may be associated with other mechanisms exhibited by transplanted cells.[34]

Reconstitution of immune system

Transplantation of HSCs can produce long-term remission by destroying the autodestructive immune system and reconstituting it in MS patients.[24]

Immunomodulation

Previous studies have demonstrated that stem cells from different sources have immunosuppressive properties. Neural progenitor cells can inhibit T-cell activation and proliferation,

Table 1 Conventional therapies for multiple sclerosis

	Possible mechanisms	Therapeutic outcomes
High-dose steroids	Anti-inflammation	Accelerates the process of recovery
	Immunosuppression	Reduces the duration of the relapse
Plasma exchange	Removing immune inflammatory substances	
Disease-modifying drugs	Immunomodulation	Reduces annualized relapse rate
		Stabilizes the Expanded Disability Status Scale
		Decreases the number of gadolinium-enhancing lesions on magnetic resonance imaging
Symptomatic management of drugs	The mechanisms of action of drugs may be different, eg, oxybutynin competitively blocks acetylcholine receptors; botulinum toxin A directly blocks the release of acetylcholine. Both improve the symptoms of bladder overactivity	Improves cognitive performance (donepezil), spasticity (baclofen, gabapentin), neurogenic bladder overactivity (oxybutynin, botulinum toxin A); reduces systemic fatigue (amantadine, modafinil); relieves paroxysmal pain (carbamazepine, gabapentin)

accompanied by suppression of proinflammatory cytokines.[35] MSCs inhibit the activation of T cells, B cells, natural killer cells, and dendritic cells.[36] MSCs modulate local allogeneic responses through the secretion of prostaglandin 2, which switches the host immune response from a T-helper (Th)-1/Th17- toward an anti-inflammatory Th2-like secretory profile.[37] U-MSCs increase regulatory T cells and reestablish the balance between Th1- and Th2-related functions.[38] Other soluble factors, such as indoleamine 2,3-dioxygenase, TGFβ1, and hepatocyte growth factor, have been implicated in the immunomodulation of B-MSCs.[34] Transplantation cells reduce the inflammatory process and ameliorate disease activity by peripheral immunosuppression.

Neuroprotective and neuroregenerative effects

A variety of evidence suggests that stem cells from different sources have the properties of neuroprotection and neuroregeneration. B-MSCs enhance endogenous neural repair in animal models of MS.[39] Neural stem cells in vivo and in vitro have been demonstrated to produce a variety of trophic factors, including NGF, BDNF, and GDNF.[40] U-MSCs secrete antioxidants, NGF, VEGF, and bFGF.[41,42] These factors may modulate the molecular composition of the environment to evoke responses from resident cells and induce axonal outgrowth, remyelination, and regeneration, and protect and rescue degenerating neurons.

Angiogenesis

U-MSCs express more genes and secrete more factors contributing to angiogenesis and neurogenesis than B-MSCs.[43] Grafted B-MSCs can differentiate into endothelial cells[44] and promote the proliferation of endogenous neural stem/progenitor cells through vascular niche regulation in injured regions.[45] Sharma et al showed that the metabolic function of many parts of the CNS significantly changed after cell treatment in patients with chronic stroke and autism.[46,47] Angiogenesis and neovascularization induced by MSCs increase cerebral blood- and oxygen-flow perfusion, thus contributing to neurorestoration.

Neuromodulation

The majority of patients with MS must endure chronic sensory and motor disabilities, such as spasticity, pain, fatigue, and tremor. Some devices of neuromodulation therapy that target the brain, cranial nerves, spinal cord, or peripheral nerves can be used to treat various refractory neurological diseases by the modulation of nervous system activity rather than the modification of damaged structure.[48,49]

Neuromodulation of the CNS

Transcranial magnetic stimulation (TMS) induces long-term excitability changes of the cerebral cortex, and has been applied to treat MS. MS patients who received intermittent theta-burst TMS[50] and repetitive TMS (rTMS)[51] had ameliorated spasticity. rTMS can also be used to treat cerebellar impairment in MS patients[52] and improve bladder dysfunction.[53] However, rTMS, as a more powerful modality, can also increase the risk of seizures.[54–56]

Motor-cortex stimulation has been confirmed to be effective for central neuropathic pain, including in MS, but higher-intensity stimulation parameters are needed to gain adequate pain relief.[57] Single-pulse TMS relieves chronic neuropathic pain in patients with various neurological diseases, including MS.

Severe tremor might be the main cause of disability in some MS patients. Deep-brain stimulation (DBS) of the thalamic nucleus ventralis intermedius can significantly reduce the intensity of contralateral limb tremor in persons with essential tremor, and thus may be considered for MS. The therapeutic effect of DBS begins intraoperatively, and can extend to the postoperative months. This treatment also partly improves activities of daily living scores without mortality or morbidity.[58] If tremors have a poor response to one DBS electrode, two electrodes may improve results.[59] However, DBS for MS tremor has often produced an unreliable and inconsistent therapeutic intervention, and has to be evaluated individually with caution.[60]

Spinal cord stimulation significantly improves bladder dysfunction, pain, and possibly spasticity in MS patients.[61] Epidural spinal cord stimulation by means of chronically implanted electrodes can provide significant long-term pain relief with improved quality of life and employment for persons with lower-limb pain caused by MS.[62]

Although disease-modifying drugs are considered mainly to suppress autoimmune activity to prevent relapse of MS, some agents have also shown neurorestorative effects. Glatiramer acetate increased BDNF production in a rat model of optic nerve damage.[63] Laquinimod significantly and persistently increased BDNF serum levels in patients with MS.[64] Neurological impairment of patients who received alemtuzumab improved for up to 6 months, and then remained stable for at least 3 years. Cultures of peripheral blood mononuclear cells from those patients contained high concentrations of BDNF, PDGF, and ciliary neurotrophic factor.[65] Both preclinical and clinical studies have demonstrated that dimethyl fumarate reduced the relapse rate and MRI activity of inflammation, and

preserved myelin, axons, and neurons via the antioxidant-response pathway.[66]

Neuromodulation of the peripheral nervous system

The implantation of a sacral neurostimulator device in patients with MS has significantly decreased urgency, frequency, upper urinary tract infections, and fever, slightly improved bowel function, and improved quality of life and emotional well-being.[67] Other clinical studies have also demonstrated that peripheral electrical stimulation of the posterior tibial nerve improves clinical and urodynamic outcome and provides long-term efficacy though suppressing neurogenic detrusor overactivity in MS patients.[68,69] However, MS patients with urinary retention due to detrusor underactivity are not suitable for this treatment.[70] The LION (laparoscopic implantation of neuroprosthesis) procedure on the sacral plexus is worth trying if the classical percutaneous technique has been unsuccessful.[71]

The gait of MS patients has been shown to significantly improve with the combination of exercise and a device that electrically stimulated the tongue to enhance the plasticity of the brain.[72]

Functional electrical stimulation (FES) produces a contraction in a paralyzed or weak muscle that can improve function through electrical excitation of the innervating nerve. FES can be used clinically to manage foot drop in people suffering from diverse neurological conditions. Patients with MS who underwent FES had significantly improved walking speed and a significant reduction in the physiological cost of gait.[73] However, a randomized trial demonstrated that the effects of exercise therapy for people with secondary progressive MS were superior to single-channel common peroneal nerve stimulation on objective aspects of gait in MS.[74]

Transcutaneous electrical nerve stimulation may relieve segmental pain by evoking paresthesia in the painful area, while central neurostimulation in contrast has been largely unsuccessful.[75]

Other approaches

Few studies have suggested that acupuncture can improve MS-related symptoms, such as fatigue, spasticity, and pain. Conclusions on the efficacy of this intervention must await further research, owing to the lack of statistical rigor and poor design in studies to date.[76] In one randomized controlled pilot trial, MS patients received massage therapy, exercise therapy, or combined massage–exercise therapy, while the control group continued their standard medical care.

The results indicated that massage therapy resulted in significantly larger improvement in pain reduction, dynamic balance, and walking speed than exercise therapy. Patients receiving combined massage–exercise therapy showed significantly larger improvement in pain reduction than those in exercise therapy.[77]

The exact mechanisms of action of neurostimulation (neuromodulation) remain unclear. They may act on different aspects of the CNS by modulating the activities of neurotransmitters and other neuroactive compounds, enhancing cortical reorganization, inducing network compensation, or increasing blood flow for promoting functional recovery in MS patients.[78–80]

Neurorehabilitation

Considerable evidence has indicated that neurorehabilitation can improve symptoms, functional capacities, and social participation.[81,82] Preliminary evidence, indicated in the following sections, suggests that efficacious neurorehabilitation may have a neuromodulatory effect. Rehabilitation interventions should be considered early for maintaining functional capacity.[83]

Physical exercise

Neurorehabilitation studies in MS have used a large range of exercises, including strengthening exercises with weight lifting, aerobics exercises on the bicycle or treadmill, and various balancing and stretching exercises. Cessation of exercise may cause recurrence of symptoms. Continuous rather than short-period exercises may be needed to support effects in patients.[84]

Fatigue is a common symptom of MS, with negative effects on various components of the patient's health and well-being. Clinical evidence suggests that exercise is superior to medication for reducing the effects of fatigue.[85] Rehabilitation interventions may also be effective in improving impairment or disability, even in MS patients who have experienced a relapse.[86]

MS patients with severely impaired ambulation have improved their muscle strength, spasticity, endurance, balance, walking speed, and quality of life after finishing locomotor body weight-supported treadmill training without fatigue or other adverse effects.[87] With or without locomotor assistance, body weight-supported treadmill training can improve gait impairment in patients with MS.[88] In a randomized trial, researchers concluded that robot-assisted gait training is feasible and safe, and may be an effective additional therapeutic option for MS patients with severe

Table 2 Neurorestorative therapies for multiple sclerosis

	Possible mechanisms	Therapeutic outcomes
Cell therapy	Reconstitution of immune system Immunosuppression Neuroprotection Neuroregeneration Angiogenesis	Improves the Expanded Disability Status Scale, suppresses inflammatory activity in magnetic resonance imaging, improves visual acuity and visual evoked response latency and the clinical symptoms and signs
Neurostimulation	Enhancing cortical reorganization Inducing network compensation Changing the excitability of neural cells Increasing the blood and oxygen flow	Ameliorates spasticity, improves bladder dysfunction and walking speed, relieves chronic neuropathic pain, reduces the intensity of limb tremor; enhances quality of life
Physical training	Immunomodulation Upregulation of expression of neurotrophic factors Increasing the blood and oxygen flow Increased CNS structural plasticity	Improves balance and coordination dysfunction, cognitive performance, spasticity, mobility, cardiorespiratory function; increases muscle strength, endurance, bone mineral density; reduces systemic fatigue, depression, and the risk of secondary diseases; enhances quality of life

Abbreviation: CNS, central nervous system.

walking disabilities.[89] However, robot-assisted step training was no better than overground walking training in patients in another randomized study.[90] Cycling progressive resistance training may improve balance, fatigue, and depression, and reduce fear of falling in patients with MS without worsening MS signs and symptoms.[91]

Constraint-induced movement therapy (CIMT) is a physical training method that has been recently adapted from the stroke field for use in MS to overcome learned nonuse, the behaviorally conditioned suppression of paretic limb use for real-life activities. CIMT combines massed practice training of the more impaired limb(s), restraint of compensatory behaviors, shaping on training tasks, and incorporating behavioral procedures to reinforce transfer of treatment effects from the clinic to the real world (behavioral contracting, home practice, maintaining an activities diary, daily problem-solving discussions with the therapist).[92] CIMT has been shown to be safe and well tolerated for progressive MS patients with either upper-extremity hemiparesis or impaired lower-extremity use.[93,94] Improvements in real-world limb use may remain for as much as 4–5 years following the single course (2 or 3 weeks) of treatment.[94,95] Moreover, a recent randomized controlled trial of upper-extremity CIMT versus a program of holistic physical complementary and alternative medicine treatments (massage, yoga, relaxation exercises, aquatic therapy) indicated superiority of CIMT not only for improving real-world paretic arm use but also for inducing increased cortical gray-matter structure on MRI,[96] thus suggesting that CIMT may have a neuromodulatory effect by stimulating structural CNS plasticity.

Each MS patient has his or her own unique physical characteristics and rehabilitation needs. As a result, adaptive personalized training should be selected to meet every patient's rehabilitation needs.[97] Physical exercise in patients with MS may contribute to neurorestoration by upregulating expression of neurotrophic BDNF, IGF, NGF, and others, which may help neuroregeneration, synaptic plasticity, neural protection, and anti-inflammatory effects.[98–100]

Cognitive rehabilitation

Fifty percent of patients with MS are estimated to have cognitive impairments resulting in considerable decline in quality of life. Cognitive intervention has been recommended to complement pharmacological treatments. Attention, information processing, and executive functions have been effectively improved in relapsing–remitting MS patients who received intensive computer-assisted cognitive rehabilitation for 3 months.[101] However, systematic reviews and meta-analyses have shown a lack of agreement concerning the efficacy of cognitive interventions for MS.[102,103]

Conclusion

This review briefly mentioned neurorestorative treatments in MS (Table 2). The treatment of MS remains a great challenge today. Conventional strategies, including steroids, disease-modifying medications, and symptomatic treatments (eg, baclofen, dalfampridine) may influence the course of MS, partly relieve the symptoms, or slow the neurodegenerative process, but they cannot halt neurodegeneration. Neurorestorative strategies not only improve the clinical course and relieve the symptoms but also promote the remodeling of CNS structure and function by neuroprotection, neuroregeneration, and immunomodulation. Early use of disease-modifying medications in combination with neurorestorative therapies may be expected to improve the prognosis of patients with severe disability. Neurorestorative treatments, alone or combined

with these different measures, should be further explored in clinical practice to provide the patient with the best help and improve quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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