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Conventional and Targeted Therapies in Multiple Sclerosis: A Narrative Review of Disease-modifying Therapies, Nanoparticles, and Exosomes

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated neurodegenerative disease of the central nervous system (CNS) characterized by inflammation, demyelination, and progressive neurological disability. Conventional disease-modifying therapies, including interferon-β, glatiramer acetate, sphingosine-1-phosphate modulators, anti-CD20 antibodies, and immune reconstitution strategies, can reduce relapse activity and disease burden; however, their efficacy is limited by adverse effects, incomplete control of compartmentalized central nervous system (CNS) inflammation, and insufficient target specificity. In parallel, nanoparticles (NPs) and exosomes have emerged as promising targeted platforms for drug delivery and immunomodulation because they may enhance blood-brain barrier (BBB) penetration and improve cell-specific delivery. This narrative review summarizes conventional and targeted therapeutic approaches in multiple sclerosis (MS), with emphasis on the translational promise and limitations of nanoparticle- and exosome-based strategies. Preclinical evidence from experimental autoimmune encephalomyelitis models and human clinical data are distinguished where appropriate. The review also highlights the major barriers that must be addressed before these approaches can be translated into routine clinical practice.

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease (Autoimmune diseases are considered a result of malfunctioning of the immune system) of the central nervous system (CNS) characterized by activating immune cells, which damages myelin and leads to demyelination, which is associated with neuronal dysfunction, loss of neurons, and axonal degeneration [1-4].

The global prevalence of MS has gradually increased, with a total of 2.8 million individuals [5]. Although the principal cause of MS remains unclear, genetic factors, such as specific mutations, inflammation, inappropriate protein aggregation (amyloid plaques), biochemical defects, such as oxidative stress and mitochondrial dysfunction, contribute to apoptosis. Environmental factors, including smoking, alcohol consumption, obesity, and viral infections, are strongly associated with the development of MS [6-8]. The main hallmark of MS is several demyelinated lesions in the white and grey matter of the brain and spinal cord [9], which are detected in the early stages of MS [10].

The different disease courses in MS are divided into four categories: (a) Relapsing-remitting MS (RRMS), (b) primary-progressive MS (PPMS), (c) secondary-progressive MS (SPMS), and (d) progressive relapsing MS (PRMS). The most common form of this disease is RRMS, in which approximately 85% of people are affected by such abnormal immunological behaviors, which are accompanied by asymptomatic periods with sudden progressions of the disease with complete or incomplete recovery. Approximately 10% of MS patients are diagnosed and placed in the primary-progressive MS (PPMS) group, in which the progression of disability is continuous, and there are temporary partial improvements. SPMS presents as an early relapsing course of disease and is characterized by progressively worsening disability with less recovery after attacks. In the PRMS group, which is the shortest course of the disease, the progression of disability is clear from the beginning, with acute relapses, with or without complete recovery, and approximately 5% of people with MS appear to be in the PRMS group at the time of diagnosis [11].

Recent studies have shown that lncRNA (long noncoding RNA) is crucial in the demyelination of nerve cells [12]. Inflammasomes, which are key elements of innate immune responses, are widely implicated in diseases characterized by inflammatory processes, such as MS [13].

Conventional treatments in multiple sclerosis

MS is an autoimmune neurodegenerative disease that leads to irreversible damage to neural tissue and dysregulation of neural function [14]. Briefly, the disruption of immune tolerance to CNS antigens and regulatory mechanisms results in the activation of autoreactive B- and T-cells [15]. Autoreactive cells enter the CNS, leading to the initiation of inflammatory responses, neuronal damage, and demyelination [15]. Therefore, conventional treatments are mainly based on strategies that include preventing the activation, migration, and inflammatory responses of immune cells and inducing regulatory or suppressive immune responses. Until the late 1980s, steroid therapy was the only approach for the treatment of MS. Since steroids do not have disease-modifying properties and only reduce clinical symptoms, the existence of specific drugs for this disease was felt [16]. In 1993, the interferon-β (IFN-β) was introduced as the first therapeutic intervention to prevent MS disease [17] by stabilizing the blood-brain barrier (BBB), inhibiting the expression of major histocompatibility complex (MHC) class II and pro-inflammatory cytokines, and up-regulation of the T helper (Th)2 response [18]. IFN-β has been approved as a disease-modifying therapy (DMT) for the clinically isolated syndrome, RRMS, and SPMS, with approximately 30% reduction in relapse rates. Afterward, more than 10 DMTs with several routes of administration, such as oral, injection (subcutaneous, intramuscular, pegylation), and infusion, have been approved by the Food and Drug Administration for the treatment of different forms of MS [19]. DMTs can alter the activation and distribution of lymphocytes by reducing T and B lymphocytes and affect the immune system [19].

Inhibiting of the lymphocytes proliferation

Another oral second-generation immunosuppressive drug that is approved and licensed for use in patients is teriflunomide, which targets semi-selective cellular processes, such as inhibition of pyrimidine synthesis in the de novo pathway on rapidly proliferating cells, affecting lymphocytes. Phase III trials have shown a reduction in relapses leading to hospitalization up to 59% at a dose of 14 mg in MS patients [20]. It is used as first-line DMT in RRMS [11, 21, 22]. Moreover, teriflunomide efficacy and safety have been demonstrated regardless of age [23].

Another drug that inhibits cell proliferation is cladribine, which acts as a DNA polymerase and ribonucleo-

tide reductase inhibitor that breaks the DNA strand and leads to the death of B and T lymphocytes [11, 21]. Of the 84 RMS patients, 72.6% had no new MRI lesions, no new relapses, and no change in expanded disability status scale (EDSS) at approximately 22 months of follow-up [24].

Targeting crucial signaling pathways

Dimethyl fumarate (DMF) is an oral disease-modifying agent used to treat RRMS [25]. DMF has different effects on immune cells, such as alteration of their composition, phenotype, and infiltration in the CNS through dependent or independent mechanisms of the erythroid nuclear factor-2-related factor 2 pathway [26]. A clinical study of 78 DMF-treated patients, with a mean 24-month follow-up, showed a 93% relapse-free condition and disease activity improvement [27]. Bruton's tyrosine kinase inhibitors (BTKIs) are a new class of MS treatments. BTKIs can cross the BBB and may attenuate chronic neuroinflammatory processes in the CNS by inhibiting adaptive and innate immune system cells both inside and outside the CNS. Recent studies have shown the effectiveness of two BTK inhibitor drugs, evobrutinib and tolebrutinib, in clinical trials, suggesting that BTKIs have therapeutic potential for MS [28, 29].

Tolebrutinib extended the time to onset of confirmed disability progression by 31% in non-relapsing secondary progressive patients during a phase 3 clinical trial (NCT04411641). The percentage of one relapse during 2 years was 14% (n=44) in relapsing MS patients after treatment with evobrutinib 75 mg once daily [30].

Targeting inflammatory cytokine

DMTs regulate the immune system, especially T-cell responses, through different strategies. In general, Th1 and Th17 are the most important myelin autoreactive T-cells that independently trigger CNS autoimmunity by regulating B-cell activation and plasma cell generation, as well as the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) [31]. Therefore, targeting the IL-12/IL-23 pathway has been considered a strategy for inhibiting pathogenic Th1 and Th17 differentiation in MS. However, unlike outcomes in experimental autoimmune encephalomyelitis (EAE), anti-IL-12/IL-23p40 antibodies have not shown therapeutic efficacy in MS patients [32], which may reflect pathway redundancy, incomplete suppression of compartmentalized CNS inflammation, and the fact that human MS is biologically more heterogeneous than the experimental model.

Immune suppression by antigen mimic

Interfering with myelin antigen presentation is another advantageous therapeutic strategy. Glatiramer acetate (GA) is a synthetic amino acid sequence that is a random mixture of four amino acids enriched in myelin, potentially binding to the MHC groove and mimicking myelin proteins [33, 34]. GA is widely used as a first-line medication for the treatment of MS disease through M2 macrophage induction, Th2 differentiation, bystander suppression, and production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) [34-37]. The exact mechanism of action of GA is not known, but it has been observed that the shift towards a neuroprotective immune response is harmless at multiple doses. In a 2-year randomized double-blind clinical trial study, GA-treated MS patients showed a reduction in the mean relapse rate by 29% compared to the placebo [38].

Inhibition of immune cells migration

Immune cell trafficking across the BBB is mediated by endothelial adhesion and signaling molecules. One of the crucial steps of the firm arrest of T-cells on the luminal surface of the inflamed BBB endothelial cells is mediated by the α4β1 integrin and its endothelial ligand, vascular cell adhesion molecule-1 [39]. In this regard, treatment with natalizumab (human anti-α4-integrin) led to fewer inflammatory brain lesions and fewer relapses over six months in patients with relapsing MS [40]. Fingolimod (FTY720) is a small molecule drug derived from myriocin, a mushroom-derived compound, and another lymphocyte trafficking blocker, a high-affinity antagonist of the sphingosine 1-phosphate receptor-1 expressed on lymphocytes, leading to their internalization and destruction, and inhibits the exit of immune cells from lymph nodes and reduces relapse in MS patients. The S1P receptor family consists of five subtypes, of which FTY720 is a non-selective modulator of S1P receptors 1, 3, 4, and 5. Siponimod (Mayzent), a selective modulator of S1P receptors 1 and 5, and Ponesimod, a selective S1P 1 receptor modulator, and two other S1P modulators are seralifimod (NCT01081782) and amislimod [41, 42]. The GOLEMS study demonstrated that 40.1% of MS patients in a 48-month period treatment by FTY720 were free of relapses [43].

Lymphocyte depletion

CD52 is a transmembrane glycoprotein that is presumed to be a common mature lymphocyte regulatory molecule [44, 45]. It has been demonstrated that CD52-targeting monoclonal antibodies (Alemtuzumab) pre-

vent demyelination, which is mediated by B- and T-cells depletion through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC); B-cells play a critical role through the production of pathogenic autoantibodies that induce cytotoxicity and damage to the CNS in a fraction of MS patients. It also leads to reduced antigen presentation, and treatment with monoclonal antibodies rituximab and ublituximab leads to a decrease in the activation of B lymphocytes [46-48]. Moreover, compared to subcutaneous IFN-β1a, alemtuzumab was more efficient in reducing annualized relapse rate, disability scores, and magnetic resonance imaging (MRI) lesion burden in RRMS patients [46]. Clinical studies showed that after 12 years, 73% of patients treated with alemtuzumab were free of MRI disease activity [46]. However, autoimmune reactions, including hyperthyroidism, immune thrombocytopenic purpura, and Goodpasture's syndrome, that have been reported with human monoclonal antibody-CD52 administration limit its clinical use [49].

B-cells play a critical role through the production of pathogenic autoantibodies, which induce cytotoxicity and damage to the CNS in a fraction of MS patients [50-54]. CD20 is a general B-cell marker expressed by the majority of B-cell populations, excluding pro-B lymphocytes, plasma blasts, and plasma cells [55]. It has been demonstrated that anti-CD20 reduces inflammatory B-cells in RRMS through the complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) [56]. Therefore, human monoclonal antibodies targeting CD20, including ocrelizumab and ofatumumab, potentially exert promising outcomes in phase II and III clinical trials of RRMS patients [57-59]. Two identical phase 3 trials, 821 and 835 patients with relapsing MS who received intravenous ocrelizumab (humanized anti-CD20 monoclonal antibody) or subcutaneous IFN-β1a, respectively, have shown that administration of ocrelizumab leads to 46% lower rates of disease activity and progression compared to IFN-β1a [57]. The results of this study were similar to the phase 2 trial of Ofatumumab (a fully human monoclonal antibody) administration to 26 RRMS patients [58].

Reset the immune system

Currently, autologous hematopoietic stem cell transplantation (aHSCT) for immune reconstitution with autologous CD34+ hematopoietic progenitor cells has been investigated as an alternative therapeutic approach for severe autoimmune diseases, such as MS [60]. In this regard, dysfunctional adaptive immune cells are depleted and eventually reconstituted with autologous stem cells collected from the MS patient prior to chemotherapy [61]. Phase II clinical trials have demonstrated that aHSCT is highly effective in the management of MS disease, such that the number of new T2 lesions was reduced by 79% or the probability of 5-year survival without progression in the expanded disability status scale (EDSS) score was estimated at 46%. [62-64]. The goal of this treatment is high-dose therapy to suppress the immune response and autoimmune inflammatory process. Infusion of aHSCT results in enhanced bone marrow recovery, halting the worsening of neurological disability, and improving neurological function. aHSCT causes inhibition of all detectable CNS inflammatory activity for a prolonged period in the absence of any ongoing disease-modifying drugs and recovery of neurological function in the phase 2 trial of 24 MS patients with poor prognosis and ongoing disease activity [63].

Targeting autophagy

Autophagy is a critical degradation process and acts as a double-edged sword in MS. By reducing oxidative stress and regulating cell proliferation, autophagy leads to increased activity of oligodendrocytes and astrocytes and prevents the progression of MS by increasing remyelination. On the other hand, overactive autophagy is associated with the progression of MS neuropathology, which causes demyelination by activating various immune cells, such as microglia and T cells. It is shown that the auto/mitophagy is associated with MS pathogenesis [88]; therefore, the use of autophagy inhibitors may reduce the pathogenesis of MS. In conclusion, autophagic activators specific to oligodendrocytes and astrocytes, and autophagic inhibitors specific to dendritic cells (DCs), microglia, and T cells exert protective effects against MS pathogenesis [67, 68].

Regulating inflammatory signaling pathways

As we know, inflammation contributes to the pathogenesis of diseases, especially autoimmune diseases. Fenofibrate is a classic drug used to treat hyperlipidemia, which is known as a peroxisome proliferator-activated receptor-α (PPAR-α) agonist. In addition to its lipid-lowering effect, it leads to the reduction of low-density lipoprotein diseases by increasing the expression of high-density lipoprotein. Therefore, fenofibrate reduces cardiovascular and anti-inflammatory effects by directly regulating inflammatory signaling pathways, such as suppressing nuclear factor-kappa-B, toll-like receptor 4, or interleukin (IL)-1 or IL-6. [69] It also directly inhibits the expression of genes associated with inflammation in inflammatory pathways and inhibits the differentiation of

helper cells (Th17). In neurodegenerative diseases, such as MS, which is a chronic inflammatory demyelinating disease of the central nervous system, fenofibrate may reduce the expression of two neuroinflammatory genes – inducible NO synthase and COX-2, and peroxisome proliferator-activated receptor-α (PPARs). It also prevents the secretion of inflammatory cytokines TNF-α, IL-1β, and IL-6 from astrocytes by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and prevents the migration of peripheral immune cells to the central nervous system by inhibiting the secretion of monocyte chemoattractant protein1 [70- 72].

Metformin is another treatment that has been considered for MS. Metformin (1,1-dimethylbiguanide hydrochloride) is a synthetic derivative of guanidine that has hypoglycemic activity and is the first drug used for the treatment of type 2 diabetes, and has anti-inflammatory, antioxidant, and anti-platelet aggregation properties. By blocking the electron transport chain, metformin inhibits the production of OXPHOS and adenosine triphosphate and causes mitochondrial dysfunction in oligodendrocytes and neurons, thereby affecting the pathomechanisms of MS/EAE. Some studies have shown that metformin reduces the course of EAE by regulating immune responses and maintaining BBB permeability. As an AMPactivated protein kinase, metformin is potentially able to protect neurons against metabolism-induced apoptosis. A significant reduction in the number of new or expanding brain lesions was observed in MS patients treated with metformin. In addition, this study showed increased expression of AMPactivated protein kinase, decreased production of IFN-γ- and IL-17, and increased percentage of Treg, T regulatory (Treg) in MS patients taking metformin. As a result, metformin is an anti-inflammatory agent and is important in myelin regeneration by increasing myelin [73].

Statins are a new therapeutic target for neurological diseases, such as MS. By reducing cholesterol levels, statins not only prevent coronary heart disease, but also have antioxidant, anti-inflammatory, and anti-platelet effects, and by inhibiting cholesterol synthesis and inhibiting the isoprenoid pathway, they induce apoptosis in glial neurons. Another important effect of statins is the inhibition of nicotinamide adenine dinucleotide phosphate oxidase, which prevents the production of superoxide in the vessels as well as in the CNS. Most patients with CNS disorders are likely to benefit to some degree from lipid-lowering therapy [74, 75].

Another activity of statins and metformin is inhibiting the expression of CD11b/CD18 receptors and thus inhibiting the coagulation factor fibrinogen. Studies have shown that fibrinogen coagulation factor plays a role in neuroinflammation and the pathogenesis of MS by stimulating microglia. Fibrinogen levels are related to the severity of MS. Consequently, inhibition of the fibrinogen cascade may reduce the neurological symptoms of MS. Fibrinogen inhibits the differentiation of oligodendrocyte progenitor cells in the brain and disrupts the remyelination process. In conclusion, inhibition of CD11b/CD18 receptor expression by metformin and statins can greatly reduce the inflammatory effect of fibrinogen on microglia, which is involved in the pathogenesis of MS. [76].

Challenges and limitations of traditional multiple sclerosis therapies

MS treatments demonstrate advantages and disadvantages depending on disease progression and patient factors. In general, conventional treatments exert immunosuppressive effects, which are associated with infections, especially herpes infections. Additionally, some adverse effects are not mediated only by immunosuppression but also reflect interference with ubiquitous physiological processes [77]. Allergic reactions, risk factors for progressive multifocal leukoencephalopathy development, bradycardia/slowing of atrioventricular conduction, macular edema, and skin malignancies are among the reported adverse effects of the therapies mentioned above [97, 98]. Natalizumab, the first antibody approved for the treatment of RRMS, has been associated with delayed infusion reactions with clinical symptoms similar to serum sickness, such as fever, headache, arthralgia, edema, and lymphadenopathy, in which treatment should be stopped immediately [78, 79]. Daclizumab binds to the IL-2 receptor and leads to a decrease in activated T cells, regulatory T cells, and natural killer cells. Common side effects of daclizumab include infection, skin rash, blood eosinophilia, meningoencephalomyelitis, and gastrointestinal and liver disorders [80]. Treatments with DMTs, such as interferon-β and GA, which are approved for MS, come with important limitations. Flu-like symptoms, depression, and fatigue have been reported with interferon-β administration, and skin reactions have been reported in patients taking GA [80]. Therefore, safer and more specific therapies are still needed to regulate the immune system in MS.

Targeted therapy in treatment of multiple sclerosis

Nanoparticle therapy

Nanoparticles (NPs) are a particular type of chemical substance with a size of approximately 10-100 nanometers [81, 82]. In general, NPs are classified into three main groups: Organic NPs (liposomes and polymers), inorganic NPs (metal, metal oxide, ceramic, and quantum dots), and carbon-based NPs (fullerene and nanotubes) [83, 84]. Interestingly, NPs are widely used in medicine due to their structure, molecular design, high surface-area-to-volume ratio, and favorable biodistribution in the body [85]. Therefore, NPs are recognized as an important tool in drug delivery, based on their specific characteristics such as improving drug solubility, preventing drug degradation, extending drug half-life, reducing non-specific binding, and delivering therapeutic agents to the specific target cells [86-88]. Furthermore, some NPs exert anti-inflammatory, anti-angiogenic, and antimicrobial properties. Over the past two decades, NPs have been used in drug development for the treatment of autoimmune diseases [89]. Current treatments for autoimmune diseases consist of anti-inflammatory drugs or non-specific suppressors of the immune system, which compromise the natural immunity against infection and cancer [89]. Surprisingly, CNS involvement and effective passage of drugs through the BBB, with reduced side effects and off-target toxicity, are considered the main challenges in the treatment of MS [90]. Interestingly, NPs are a potential therapeutic tool for the treatment of MS by targeting immune cells and stem cells with favorable effects such as penetrating the BBB and target cells, facilitating the regeneration of nerve cells, and promoting the survival, growth, maturation, and differentiation of neurons [91]. One of the most studied NPs in this field is gold nanoparticles (GNP), which, with their anti-inflammatory and anti-oxidant properties, brought promising results for the treatment of neurological diseases [91]. GNP could also lead to improved neuronal function through its electrical conductivity features. In total could be mentioned that GNPs improve the function and regeneration of axons and damaged neural cells in degenerative diseases [91]. Because of their functionality and optical and electrical properties are attractive nanomaterials in nanoscience and are widely investigated and applied in various fields [92]. Studies showed that GNPs could have notable effects on the improvement and alleviation of inflammation in EAE mice through decreasing infiltration of inflammatory immune cells to CNS white matter, downregulation of inflammatory cytokines (e.g IL-23), and upregulation of anti-inflammatory cytokines (such as IL-1β, IL-17, IL-23, IL-27), reduction of demyelination, and amelioration of clinical scores [92, 93]. To increase Treg cells differentiation in EAE, the usage of GNPs loaded with myelin antigen and a ligand for aryl hydrocarbon receptor (AHR) activation to induction tolerogenic DC cells and subsequently Treg cells differentiation has shown acceptable outcomes [94].

Considering the role of myeloid cells, such as macrophages and DCs, in the pathogenesis of MS, targeting these cells can be considered a therapeutic aim in MS immunotherapy [95]. Since NPs larger than 100 nm can be taken up by myeloid cells, treatment of EAE mice with 500 nm poly (lactic-co-glycolic acid) (PLGA) improves inflammation by reducing inflammatory monocytes and DCs in the spleen and CNS, through apoptosis or changing the inflammatory phenotype to a regulatory phenotype [95]. Moreover, antigen-specific immunotherapy to DCs-specific tolerance induction by using biomimetic NPs alleviates EAE or MS [96]. In another study, PLGA NPs coated with myelin peptide-MHC complex, programmed death-ligand-1, anti-Fas regulatory molecules, CD47 self-marker, and tumor growth factor-β (TGF-β1) inhibitory cytokine to interact with Antigen-specific autoreactive T cells [96]. These NPs inhibit the proliferation of autoreactive T cells, induce the differentiation of the regulatory phenotype (Treg cells), and secrete anti-inflammatory cytokines in EAE mice. Also, GNPs loaded with myelin antigen and a ligand to activate the AHR to induce tolerogenic DCs and subsequently differentiate Treg cells have shown promising results in EAE [94]. In another study, the immunomodulatory potential of NPs-liposomes, constituted by a double-layer of phosphatidylserine (PSCho/PS), and double-faced, with an outer layer of phosphatidylserine and an inner layer of phosphatidic acid (PSCho/PA), either alone or in the presence of the myelin basic protein (MBP) peptide, was investigated in patients with MS [97]. These NPs reduce Th1 and Th17 pro-inflammatory lymphocytes and cause a change in the ratio of pro-inflammatory/anti-inflammatory macrophages (M1/M2) [97]. On the other hand, in a phase I randomized, double-blind, placebo-controlled clinical trial study using PEGNLPUOs NPs, showing a decrease in the level of matrix metallopeptidase-9 (MMP-9), the level of Th2 cytokines, the number of relapses, disability scores, and T2 lesions in patients with MS [98]. In a recent study, gold NPs conjugated with Contactin-related protein (Caspr) antibodies were used to target neuronal cells, which reduced the severity of MS symptoms in EAE [99]. The Caspr family is a transmembrane protein that participates in nerve excitation and conduction, and neurotransmitter release in myelinated axons [100]. Moreover, the timing of neuron and astrocyte differentiation in neural progenitor cells is

Table 1. Studies conducted on the therapeutic effect of NPs in experimental autoimmune encephalomyelitis and MS disease

NPs	Experimental Model	Mechanism	Ref.
CeNPs-decorated MSN-MOG	EAE	- MSN-MOG vaccine suppressed CNS-infiltrating APCs and CD4+ T cells - ROS-scavenging CeNPs suppresses activation of APCs and induces tolerogenic APCs	[134]
PLGA-LABL-MOG	EAE	- Decrease in inflammatory cell infiltration and the demyelination - Reduced MHC II and the co-stimulatory molecule CD86 expression of DCs	[136]
DMF- loaded SLN	EAE	- Increased influx of Foxp3+ cells into the spinal cord	[137]
LIF-PLGA-CD4	EAE	- Induction antigen-specific self-tolerance - Increase in Treg phenotype	[138]
IL-13 loaded XL-MSNs	EAE	- Protection of IL-13 degradation - Alternative activation of MQ - Regulation of immune cell infiltration	[139]
AhR agonist loaded NLPs	EAE	- Reduction of T eff infiltration CNS - Induction of tolerogenic DCs	[140]
ChABC@PSi	EAE	- Effective CSPGs digestion - Increase the number of newly generated oligodendrocyte lineage cells - Enhancement of myelin repair	[141]
TFM-MNLC	EAE	- Rapid remyelination - Increase entrapment efficiency	[142]
GNPs and PEG	EAE	- Reduction of cells' infiltration and demyelinated lesions - Alteration in levels of IL-23 and IL-27	[143]
Nanocurcumin	RRMS patients	-Increased frequency of Treg cells and expression of FoxP3 -Increased levels of the TGF-β and IL-10	[144]

Abbreviations: Mog: Myelin oligodendrocyte glycoprotein; CNS: Central nervous system; CSPGs: Chondroitin sulfate proteoglycans; EAE: Experimental autoimmune encephalomyelitis; FOXP3: Forkhead box P3; RRMS: Relapsing-remitting MS.

mediated by Caspr [101]. The expression of Caspr1 associated with some neurodegenerative diseases mainly appears on the neuronal surface following demyelination [100]. Therefore, it could be represented as a therapeutic target for treatment [101, 102].

Gold NPs conjugated with Caspr antibodies showed a decrease in demyelination and infiltration of immune cells and an increase in regulatory T cells [99]. Conjugating the desired drugs with the antibody against Caspr can help target damaged myelin. Another advantage of drug targeting is that it prevents their deposition in tissues other than the CNS, such as the kidney. Eventually, remyelination is another strategy in the treatment of MS that has shown promising results in the EAE model. PLGA NPs encapsulated with leukemia inhibitory factor (LIF) promote remyelination by inducing the maturation of oligodendrocyte progenitor cells (OPCs) [103].

Table 1 presents other examples of the use of NPs in the treatment of EAE and MS.

Exosome therapy

Exosomes are 30 to 150 nm vesicles that are physiologically secreted from different cell types, including epithelial cells, mast cells, B and T-cells, DCs, and nerve cells [104, 105]. Exosomes can be identified using cell surface diagnostic markers such as tetraspanins CD63, CD9, CD37, CD81, and TSG101 [106-108]. Recent studies have shown that the number of exosomes varies in different conditions, especially pathological states [109]. Exosomes are important in intercellular communication through the transportation of proteins and functional microRNAs [110, 111]. Exosomes have several mechanisms to interact with target cells, especially cell-to-cell communication. In general, exosomes are attached to the cell membrane of the target cell and transfer their cytoplasmic contents as well as surface proteins [112]. It is noteworthy that exosomes have an intrinsic ability to cross biological barriers. It has been shown that tumor-derived exosomes and microvesicles are able to cross the BBB in mice bearing glioma or from the circulation of glioblastoma patients [113]. Therefore, exosomes can be considered potential carriers for drug delivery. In addition, it has been shown that the combination of drugs with exosomes increases the drugs' half-life and maintenance of the therapeutic activity and improves the delivery of the drug to the brain [98, 114-116]. Moreover, exosomes were used for systemic delivery of small interfering RNA to cross biological barriers [116, 117]. Recently, it has been found that the passage

of NPs through the BBB and their transfer to the brain is accelerated with the combination of exosomes [114, 118].

Today, the existence of more than 2300 types of proteins and 270 types of microRNA in exosomes has been proven [119]. Evidence has shown that the substances enclosed in exosomes depend on the type of maternal cell and production conditions. Among the contents of exosomes, we can mention things, such as hepatocyte growth factor, IL10, IL6, TGFβ1, MMP-9, vascular endothelial growth factors, and a variety of microRNAs that show inflammatory and anti-inflammatory properties [120-122]. Meanwhile, anti-inflammatory cytokines, such as IL-10 and TGF-β, potentially suppress the immune system and can be used in the treatment of autoimmune diseases, i.e. MS disease.

The findings showed that exosomes can be used as a cell-free method for autoimmune treatment. Mesenchymal stem cells (MSCs)-derived exosomes have been shown to have an inhibitory effect on RRMS-derived peripheral blood mononuclear cells, similar to that of MSCs [123]. In addition, IFNγ-stimulated-MSCs derived exosomes affect the treatment of EAE. Another finding indicated that MSCs-derived exosomes cause a change in the M1/M2 ratio in favor of the M2 phenotype and reduce the clinical features of EAE [124]. Besides, intranasal injection of IFN-stimulated DCs derived exosomes (IFNγ – DC – Exos) can improve brain myelination in vivo [125]. The employment of exosomes derived from DCs with overexpression of TGF-1 in EAE treatment leads to increased Treg production and suppression of Th1 and Th17 differentiation [125, 126]. Moreover, studies showed that exosomes from pregnant mice reduced the demyelination and the infiltration of inflammatory cells into the spinal cord in EAE mice. Also, an increase in the CD4+ CD25+ FoxP3+ Treg, beside decrease the expression of miR-326 and inflammatory cytokines such as IL17 and IFN-γ, was observed in exosomes-treated mice. Therefore, exosomes from pregnant mice can be used as a therapeutic approach in EAE by modulating the balance of Treg/Th17 [127]. Interestingly, intranasal administration of resveratrol-loaded macrophage exosomes, a natural polyphenolic compound targeting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) with potent anti-inflammatory properties, significantly inhibited inflammatory responses in the CNS and peripheral system in EAE and effectively improved the clinical evolution of MS in vivo [128]. Recently, it has been shown that the surface of extracellular vesicles could be used to functionalize NPs that could pass through the BBB unharmed and reach the brain [129]. Accordingly, treatment of EAE mice with exosome-combined GNPs showed the reduction of inflammation and nerve cell repair, which subsequently leads to the improvement of clinical symptoms. These results showed a significant increase in the number of Tregs and a decrease in the production of pro-inflammatory cytokines in the spleen of EAE mice treated with exosome-combined GNPs [99]. Although the use of exosomes can be beneficial in the treatment of MS, their low targeting ability and size-dependent cellular uptake can severely affect their delivery [88]. Therefore, recent studies have concentrated on engineered exosomes with increased efficiency and effectiveness. Studies showed that intranasal administration of brain-derived neurotrophic factor by brain-targeted engineered exosomes was a highly effective delivery route to the brain that had a significant therapeutic effect on myelination and motor coordination in a demyelination mouse model [130]. Besides, engineered exosomes carrying the anti-inflammatory cytokine IL-4 from a microglial cell line significantly reduce the clinical score of EAE [131]. Also, forkhead box P3 (FOXP3)-transfected DCs exosomes can inhibit the differentiation of Th1 and Th17 cells, promote the Treg cells production, and ameliorate the development of EAE by regulating the Th/Treg balance [132]. Moreover, delivery of bryostatin-1 by modified exosomes with the ability to target OPCs significantly improves the protection of the myelin sheath and promotes remyelination [133].

Table 2 presents other examples of the therapeutic and inhibitory effects of exosomes in EAE.

Clinical translation and challenges

Although nanoparticle- and exosome-based therapies have shown great promise in preclinical studies, their translation to human MS remains challenging. The EAE model is valuable for defining inflammatory mechanisms and testing proof-of-concept interventions; however, it does not fully reproduce the chronicity, lesion heterogeneity, compartmentalized central nervous system inflammation, intrathecal immune activity, or progressive neurodegeneration observed in human disease. In addition, EAE is usually induced in genetically or immunologically homogeneous animals at a synchronized disease stage. In contrast, human MS evolves over years in a biologically diverse population with distinct genetic backgrounds, environmental exposures, disease courses, and treatment histories. Therefore, robust efficacy in EAE should be interpreted as hypothesis-generating rather than as direct evidence of clinical efficacy in patients.

Table 2. Studies on the therapeutic and inhibitory effect of exosomes in experimental autoimmune encephalomyelitis

Exosome	Experimental Model	Results	Ref.
MSC-Exo (exosomes derived from rhesus monkey MSCs)	EAE CPZ	- Increase in numbers of newly generated OLs, mature OLs, and the level of MBP - Promotion of remyelination and polarization of M2 phenotype - Blocking of TLR2 signaling	[145]
MSC-derived exosomes	SOD1G93A EAE	- Downregulating TNF and IL1b expression by miR-467f and miR-466q - Modulating pro-inflammatory phenotype of microglia by inhibition of expression of miR-467f and miR-466q target genes (*Map3k8* and *Mk2*)	[146]
M2- derived exosomes	EAE	- Decrease in inflammatory factors and TH17 - Alleviation of EAE symptoms by upregulating SOCS5 and inactivating the JAKs/STAT3 pathway	[147]
i35-Bregs- derived exosomes	EAU	- Expansion of IL-10 and IL-35 secreting Treg cells - Suppression of Th17 responses - Absence of toxicity or alloreactivity associated with exosomes	[148]
IFNγ-stimulated MSCs-derived exosomes	EAE	- Reducing demyelination and neuroinflammation - Upregulating the number of Tregs - Immunosuppressive effects by Anti-Inflammatory and Neuroprotective Proteins such as HSP70, Gal-1, and PD-L1	[175]
LJM-3064 aptamer-exosome bioconjugate	OLN93 (in vitro model) EAE	- Promoting the proliferation of oligodendroglia cell line - Suppression of inflammatory response and demyelination lesion in CNS	[150]
BMSCs- derived exosomes	EAE	- Increasing the levels of M2-related cytokines - Decreasing M1-related - Attenuating inflammation and demyelination of the CNS by regulating the polarization of microglia	[151]

Abbreviations: SOCS5: Suppressor of cytokine signaling 5; TNF-α: Tumor necrosis factor-α; PDL-1: Programmed death-ligand-1; M1/2: Macrophages; EAE: Experimental autoimmune encephalomyelitis.

From a translational standpoint, nanotherapeutics and exosomes face a second layer of barriers beyond biological validity. These include reproducible large-scale manufacturing, batch-to-batch consistency, sterility, long-term storage stability, cargo-loading efficiency, controlled release, pharmacokinetic predictability, and precise biodistribution after systemic administration. Protein corona formation, opsonization, uptake by the reticuloendothelial system, off-target sequestration in the liver and spleen, and incomplete penetration across the BBB can all reduce the fraction of administered material that actually reaches the pathological compartment in the CNS. Even when brain entry is achieved, endosomal escape, intracellular trafficking, and sustained functional cargo release remain unresolved challenges.

The clinical failure of some pathway-directed therapies in MS can be explained mechanistically by disease complexity rather than a lack of biological plausibility. For example, neutralizing a single cytokine axis may be insufficient when redundant inflammatory circuits, compartmentalized meningeal and parenchymal inflammation, microglial activation, and neurodegenerative cascades coexist. Likewise, therapies that are effective when administered early may appear neutral in late-stage disease because irreversible axonal loss and glial scarring have already accumulated. In addition, inadequate target engagement within the CNS, poor patient stratification, insensitive clinical endpoints, and follow-up periods that are too short to capture disability progression can obscure a true biological signal. Therefore, translational success will depend not only on improved delivery systems, but also on biomarker-guided patient selection and trial designs that are better aligned with the underlying biology of MS.

In summary, nanotherapeutics and exosomes offer a compelling platform for more selective, CNS-directed intervention in MS; however, their success will depend on overcoming biological, technical, and regulatory barriers. A translational strategy that combines improved delivery, rigorous patient selection, and biomarker-driven evaluation is likely to provide the strongest path toward clinically meaningful benefits.

Future directions

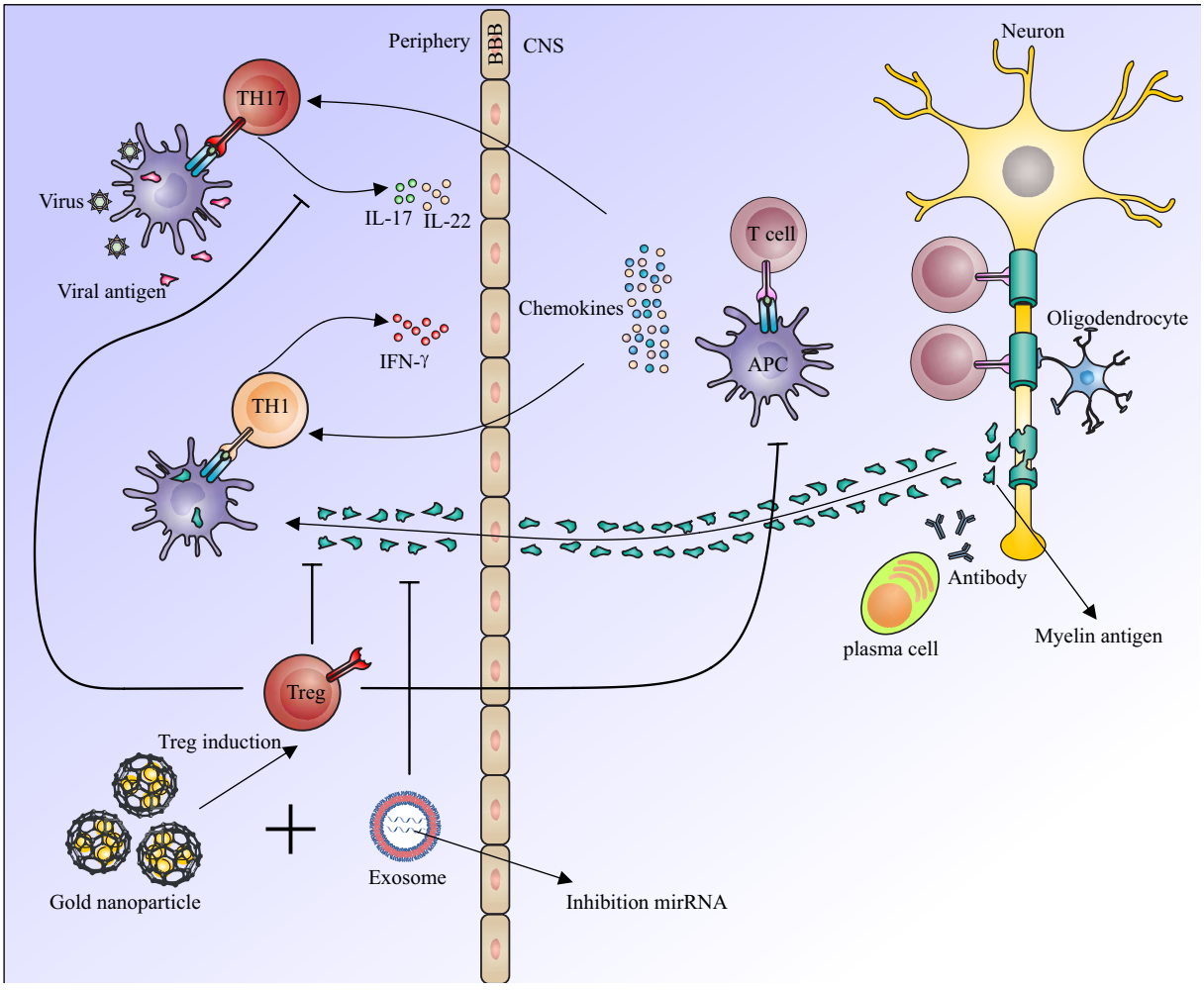

Figure 1. The therapeutic and inhibitory effect of G NPs and exosomes in multiple sclerosis disease

Future work in MS focuses on precision-oriented and mechanistically informed therapeutic design. The most promising direction is not simply to increase the potency of a single platform, but to engineer delivery systems that are matched to disease stage, immunologic endotype, and anatomic compartment. Biomarker-guided stratification using neurofilament light chain, MRI-based lesion activity, CSF immune signatures, and peripheral transcriptomic or proteomic markers may help identify patients who are most likely to benefit from a specific nanoparticle or exosome-based intervention. Future nanotherapeutics should combine cell-specific targeting ligands, stimuli-responsive release, and cargo designs that can simultaneously suppress inflammation and promote remyelination. Engineered exosomes are particularly attractive because they can be functionalized with defined surface molecules, loaded with regulatory RNAs, anti-inflammatory proteins, or remyelination-promoting factors, and administered through routes, such as intranasal delivery, which may enhance CNS access. Hybrid platforms that integrate synthetic NPs with biological vesicles may further improve stability, specificity, and transport across the BBB.

Another priority is translational robustness. Standardized good manufacturing practice protocols, potency assays, release criteria, and stability testing are essential before these platforms can confidently advance into clinical trials. Equally important is the development of adaptive trial designs that allow earlier go/no-go decisions, incorporate harmacodynamics biomarkers of target engagement, and distinguish symptomatic improvement from true disease modification. Combining nanotherapeutics or exosomes with existing disease-modifying therapies may also be valuable, provided that immunologic synergy and safety are carefully evaluated. In this framework, the future of MS treatment is likely to depend on integrated approaches that unite delivery science, immunology, neurobiology, and precision medicine.

Conclusion

MS is an autoimmune and neurodegenerative disease that causes disability in young adults. There is no definitive cure for MS, but several studies have developed appropriate therapeutic targets and disease-modifying agents. Common treatments suppress the immune system by inhibiting pathogenic cytokines, antigen presentation, or immune cell migration to reduce immune responses and MS damage. However, these treatments are associated with viral infections in the CNS. Therefore, identifying a treatment with low toxicity is of paramount importance. Recent advancements in MS treatment have been quite promising and innovative. Their focus is on increasing DMT efficacy, remyelination, and neuroprotection, resetting the immune system through aHSCT, and a cell-free therapies approach. These advancements reflect efforts to develop more effective and safer treatments. NPs and exosomes are well-known cell-free treatments that can reduce the risk of immune rejection and side effects. These approaches potentially improve the immune system and reduce CNS inflammation. Additionally, among NPs, GNPs have been widely investigated, and it has been reported that GNPs have anti-inflammatory and antiapoptotic effects, which improve neurological defects. Moreover, GNPs showed immunosuppressive effects, which significantly reduced Th1 and Th17 infiltration into the CNS, and raised Treg and Th2 cells in EAE models. In addition, the co-delivery of tolerogenic molecules by GNP-mediated suppressed EAEs through the induced tolerogenic DCs promoted the differentiation of Tregs. Furthermore, GNPs can preserve human neural stem cells from β-amyloid protein injury and decrease mitochondrial damage by regulating the miR-21-5p/SOCS6 pathway. Interestingly, different shapes and sizes of GNP have distinct effects on innate immune responses, which can activate or suppress inflammasome signaling, antigen processing, and presentation. On the other hand, different coatings and GNPS sizes can regulate T cell and B cell function in different ways. As mentioned, GNPs are potential new treatments for autoimmune disorders, and the coating of therapeutic agents on the GNP surface promotes the therapeutic properties of drugs and their delivery. In addition, the combination of these methods with different treatment strategies has shown promising effects. CASPR protein is considered a specific candidate for target therapy that potentially mediates the tracking of damaged neurons. By targeting this protein in combination with NPs and exosomes, especially GNPs, it is possible to deliver drugs to the damaged cells in a more targeted manner and to reinforce the remyelination and regeneration of damaged cells alongside the prevention of their deposition in other tissues. Also, combining GNPs with exosomes can improve the delivery of NPs to the nervous system, in addition to taking advantage of the immune regulatory properties of exosomes. Figure 1 shows the therapeutic and inhibitory effects of GNP and exosomes in MS.

Ethical Considerations

Compliance with ethical guidelines

This article is a review paper with no human or animal sample.

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Authors contribution's

Conceptualization: Shirin Taghizadehand and Mir Hadi Jazayeri; Methodology: Shirin Taghizadeh, Melika Gorgani, Gilda Parsamanesh, and Mir Hadi Jazayeri; Supervision and writing the original draft: Shirin Taghizadeh; Review and editing: Shirin Taghizadeh, Melika Gorgani, Gilda Parsamanesh, and Hamid Nickho; Visualization: Hamid Nickho.

Conflict of interest

The authors declared no conflict of interest.

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