REVIEW ARTICLE

Recent Advances on Immunosuppressive Drugs and Remyelination Enhancers for the Treatment of Multiple Sclerosis

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Abstract: Mammalian nervous systems depend crucially on myelin sheaths covering the axons. In the central nervous system, myelin sheaths consist of lipid structures that are generated from the membrane of oligodendrocytes (OL). These sheaths allow fast nerve transmission, protect axons and provide them metabolic support. In response to specific traumas or pathologies, these lipid structures can be destabilized and generate demyelinating lesions. Multiple sclerosis (MS) is an example of a demyelinating disease in which the myelin sheaths surrounding the nerve fibers of the brain and spinal cord are damaged. MS is the leading cause of neurological disability in young adults in many countries, and its incidence has been increasing in recent decades. Related to its etiology, it is known that MS is an autoimmune and inflammatory CNS disease. However, there are no effective treatments for this disease and the immunomodulatory therapies that currently exist have proven limited success since they only delay the progress of the disease. Nowadays, one of the main goals in MS research is to find treatments which allow the recovery of neurological disabilities due to demyelination. To this end, different approaches, such as modulating intracellular signaling or regulating the lipid metabolism of OLs, are being considered. Here, in addition to immunosuppressive or immunomodulatory drugs that reduce the immune response against myelin sheaths, we review a diverse group of drugs that promotes endogenous remyelination in MS patients and their use may be interesting as potential therapeutic agents in MS disease. To this end, we compile specific treatments against MS that are currently in the market with remyelination strategies that have entered into human clinical trials for future reparative MS therapies. The method used in this study is a systematic literature review on PubMed, Web of Science and Science Direct databases up to May 31, 2020. To narrow down the search results in databases, more specific keywords, such as "myelin sheath", "remyelination", "demyelination", "oligodendrocyte" and "lipid synthesis" were used to focus the search. We preferred papers published after January 2015, but did not exclude earlier seminal papers.

Keywords: Multiple sclerosis, myelin sheath, remyelination, demyelination, oligodendrocyte and lipid metabolism.

1. INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory disease that damages myelin in the central nervous system (CNS), causing neurological deterioration and, in many cases, severe disability. It is a common neurological disease that affects about 2.3 million people worldwide [1] and it is the leading cause of neurological disability in young adults in many countries. Its incidence has been increasing in recent decades. Most MS patients suffer from clinical episodes of inflammatory demyelination (relapse) followed by periods of variable recovery and relatively clinical stability (RRMS).

Related to its etiology, MS is considered an autoimmune demyelination disorder in which activated T cells migrate through the blood-brain barrier and attack the myelin sheaths that surround axons. This leads to progressive demyelination of the axons, which ultimately culminates in the degeneration of the neurons (secondary progressive MS, SPMS). Acute inflammatory lesions are characterized by the presence of activated T cells (both CD4 and CD8) and axonal damage is associated with the degree of inflammation. The inflammation is initially transient and axon remyelination occurs, which may explain the relapsing-remitting nature of RRMS signs and symptoms. If demyelination persists, myelin-free axons are vulnerable to damage, and these attacks mediated by the immune system itself lead to axonal injury and neuronal death [2].

The ability of the CNS to reshape the myelin that surrounds the axons influences the connectivity and functioning of neural circuits. Unfortunately, the age of an organism may negatively affect this process due to alterations in metabolism, inflammation processes or especially myelin diseases. These alterations contribute to the loss of support offered by the oligodendrocytes (OLs), cognitive deterioration and neurodegeneration [3].

2. MULTIPLE SCLEROSIS GENETIC RISK FACTORS

Although the nature of MS remains elusive, it has been reported that MS implies a complex interaction between environmental and genetic factors. Several environmental factors have been identified to play a role in MS, including lack of vitamin D [4], and Epstein-Barr virus (EBV) exposure [5]. Concerning genetic factors, large genome-wide association studies (GWASs) have identified more than 200 risk genes associated with MS [6]. Among them, most with a link to immune function [7], identified as susceptibility factors, the strongest associations are with the HLA-DRB1 (human leucocyte antigen) locus in the major histocompatibility complex (MHC), which encodes a molecule that presents peptide antigens to $CD4^+$ T lymphocytes [8]. Additional genetic risk variants include *CD80* and *CD86*, which are the binding partners of co-stimulatory (*CD28*) and co-inhibitory (*CTLA4*) molecules expressed on T cells. Non-HLA genes have also been indicated to contribute to genetic susceptibility, in particular, four genes (*PXT1*, *ZMIZ1*, *EOMES* and *TRAF3*) linked to EBV [9], two genes (*CYP27B1* and *CYP24A1*)

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Table 1. Overview of specific treatments against MS currently in the market.

Compound	Mode of Action	Currently in Clinical Practice / Clinical Trials / Preclinical Research	Drug Name® and Company
Alemtuzumab	Humanized monoclonal antibody against CD52, which is a surface molecule predominantly expressed on B an T cells	Used in clinical practice for highly active RRMS.	Lemtrada / Sanofi-Aventis
Ocrelizumab	Recombinant humanized IgG1 monoclonal antibody against CD20, which exist principally in B cells	Used in clinical practice for RRMS and PPMS.	Ocrevus /Roche
Cladribine	Purine analogue taken up rapidly by proliferating cells like lymphocytes.	Used in clinical practice for RRMS.	Leustatin /Johnson & Johnson
Teriflunomide	It inhibits dihydro-orotate dehydrogenase (enzyme in the de novo pyrimidine synthesis pathway), which leads to a reduction in the proliferation of activated T and B lymphocytes	Used in clinical practice for RRMS.	Aubagio / Sanofi-Genzyme
Mitoxantrone	Inhibitor of type II topoisomerase which induces cell lysis and initiation of programmed cell death in proliferating B and T lymphocytes	Used in refractory and highly active MS due to important side effects.	Mitoxantrone /Sandoz
Fingolimod	Sphingosine-1-phosphate-receptor modulator	Used in clinical practice as a second-line therapy for highly active and refractory RRMS and SPMS due to important side effects.	Gilenya / Novartis
Siponimod	S1PR antagonist; blocks lymphocytes egression.	Used in clinical practice for RRMS and SPMS.	Mayzent /Novartis
Ozanimod	S1PR antagonist; blocks lymphocytes egression.	Used in clinical practice for highly active RRMS.	Zeposia / Celgene
Natalizumab	A monoclonal antibody, blocks the α4β1 subunit of integrin molecules on leukocytes, that inhibits leukocyte extravasation into the CNS	Used in clinical practice as a second-line therapy for RRMS with other DMDs .	Tysabri / Biogen
β-interferon	Type I interferon participates in the regulation of the immune system	Used in clinical practice for RRMS.	Betaferon / Bayer Healthcare Extravia / Novartis Avonex / Biogen EMD Serono / Pfizer
Glatiramer acetate	A mixture of random synthetic polypeptides. The mode of action in MS is not completely understood	Used in clinical practice for RRMS.	Teva's Copaxone

controlling the metabolism of vitamin D [10], five genes linked to astrocyte function (*CLEC16A*, *IL22RA2*, *TNFRSF1A*, *CYP24A1* and *PHGDH*), three genes (*OLIG3*, *ZNF365* and *BCAS*) key to oligodendrocyte function [11], a gene (*CNR2*) codifying a cannabinoid receptor and several other genes (*i.e*. *COXM1*, *WWOX*, *PRDX5*, *IPYR2*, *CYB* and *ALDH2*) linked to oxidation-reduction and the electron transport chain, which support previous studies that highlight the electron transport chain as a dysregulated pathway in MS lesion. Although drug targets with genetic support are most likely therapeutically valid [12], only very few of these genes have been pursued as drug targets and even fewer taken into clinical trials (ipilimumab for *CTLA4* and cannabidiol for cannabinoid receptor 2, *CNR2*) [13], [14]. However, analysis of current agents used to treat MS (see next sections) correlates with the information that GWAs provides and underscores the rationale for approaches that target B and T cells (such as CD20-targeted antibody, ocrelizumab, CD52-targeted antibody, alemtuzumab), modulate immune system (such as β-interferon or cladribine), astrocyte and oligodendrocyte functions (such as simvastatin and clobetasol), vitamin metabolism, and/or electron transport chain as efficient therapies.

3. IMMUNOSUPRESIVE DRUGS FOR THE TREATMENT OF MS

Nowadays, although there is not yet a cure for MS, there are medications that help to manage the disease. Here, we summarize a list of immunosuppressive or immunomodulatory drugs that reduce the immune response against myelin sheaths. These compounds mainly act by regulating the number of lymphocytes, their proliferation, their trafficking or the production of cytokines. An overview of specific treatments against MS that are currently in the market is provided in Table **1**.

3.1. Drugs Targeting B And T Cell Survival

Alemtuzumab is a humanized monoclonal antibody against CD52, which is a surface molecule predominantly expressed on B and T cells. Its use was approved by Food and Drug Administration (FDA) in 2014 in over 62 countries for RRMS therapy [15]. Alemtuzumab leads to a rapid and long-lasting depletion of CD52 positive cells, followed by a slow repopulation arising from unaffected hematopoietic precursor cells. CD52 is a glycosylphosphatidylinositol (GPI)-anchored protein implicated in the activation and migration of T lymphocytes [16]. Although alemtuzumab depletes lymphocytes in most individuals, in some people, it fails to deplete or deplete poorly, probably due to variations in biological response and naturally occurring antibodies (NAbs), leading to treatment failure [17].

Ocrelizumab is a recombinant humanized IgG1 monoclonal antibody against CD20 surface protein. It was approved as a treatment for RRMS and PPMS by the FDA in 2017 and the European Medicines Agency (EMA) in 2018. Ocrelizumab depletion affects principally pre-B cells, mature B cells and memory cells, preserving stem cells and plasmatic cells as CD20 is not expressed on their surface and therefore maintaining humoral and innate immune response [18]. Depletion of B cells occurs *via* antibody-dependent cell-mediated phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. In particular, ocrelizumab shows a more focused ADCC and a lower CDC effect compared to rituximab since ocrelizumab targets the large extracellular loop of CD20 [19].

3.2. Drugs Targeting B and T Cell Proliferation

Cladribine (2-Chlorodeoxyadenosine) is a disease-modifying drug that depletes B and T lymphocyte levels. It is used in the treatment of inflammatory and immunological diseases. Due to the im-

munological base pathogenesis of MS, cladribine has been used as an effective therapy for relapsing-remitting multiple sclerosis (R-RMS) in both parenteral and oral formulations. Cladribine is a purine analogue, it is taken up into rapidly proliferating cells like lymphocytes to be incorporated into DNA synthesis. Unlike adenosine, cladribine has a chlorine molecule at position 2, which renders it partially resistant to breakdown by adenosine deaminase (ADA). Deoxycytidine kinase (DCK) transforms cladribine by phosphorylation, forming cladribine-triphosphate (CdATP) and inducing cellular apoptosis [20], [21] through disrupting DNA synthesis and repair and altering mitochondrial permeability [22]. As B lymphocytes express higher levels of DCK and lower levels of ADA compared to T cells, the cellular depletion is focused on B cells [20], [22]. CD8+ lymphocytes and innate immune response cells have a lower CDK, which provides protection against cladribine cytotoxicity and maintains certain immune activity [21], [23].

Teriflunomide selectively and reversibly inhibits dihydro-orotate dehydrogenase (DHODH), a key mitochondrial enzyme in the de novo pyrimidine synthesis pathway, leading to a reduction in proliferation of activated T and B lymphocytes without causing cell death. It was approved in 2013 by FDA. It inhibits the production of IL-17, TNF-alpha, protein tyrosine kinases, the NF-kB pathway, and the IgG secretion of activated B cells, and interferes with the kynurenine pathway [24], [25], [26]. It also induces apoptosis of EBV-transformed B cells [27].

Mitoxantrone is an inhibitor of type II topoisomerase, which induces cell lysis and initiation of programmed cell death in proliferating B and T lymphocytes [28] [29]. Mitoxantrone was the first drug approved by the FDA and several European countries to treat worsening RRMS, SPMS and PPMS. As it was primarily developed as a cytotoxic treatment for acute myeloid leukemia, this produces several adverse events as cardiotoxicity and colon cancer [30]. For this, the use of mitoxantrone has decreased due to the risk of these severe adverse events and the introduction of novel therapies. The agent should be restricted to selected patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability for whom no alternative treatments [31] are available.

3.3. Lymphocyte Trafficking Drugs

Fingolimod (FTY720) is a functional antagonist of sphingosine-1 phosphate receptor 1-3,4,5 (S1PR1 being the dominant receptor in lymphocytes) [32]. It binds to the receptor, leading to internalization of the S1P/S1PR complex *via* the ß-arrestin-mediated mechanism [33] and thereby preventing the egress of lymphocytes [32]. It has been approved by the FDA for CIS (clinically isolated syndrome), RRMS and active SPMS in 2010. It has many adverse events as bradycardia, lymphopenia, macular edema or infections. Recent trials have investigated more receptor-specific agents targeting S1PRsin, trying to mitigate the side effects. A modification of Fingolimod is Siponimod (a selective S1P1/S1P5 binding agent), which produces fewer episodes of bradycardia [34]. It was approved as Mayzent® by the FDA in 2019.

Natalizumab was the first monoclonal antibody approved in 2004 for RRMS treatment. It is a humanized recombinant IgG4 monoclonal antibody that inhibits leukocyte extravasation into the CNS and intestinal tract by blocking the α4 subunits of integrin molecules on leukocytes [35]. Integrins are cell surface glycoproteins that facilitate cell-matrix adhesion and mediate leukocyte rolling and adhesion to the endothelium prior to extravasation [36]. By inhibiting their interaction with a vascular cell-adhesion molecule (VCAM)-1 expressed on endothelial cells, natalizumab prevents T lymphocytes from crossing the BBB, thereby reducing inflammation in the brain tissue compartment [37].

3.4. Drugs Modulating Immune System

ß-interferon (IFNß) belongs to the class of type I interferons and is produced by lymphocytes, fibroblasts, macrophages and endothelial cells [38]. Interferons play an important role in the regulation of the immune system. The effects modulated by IFN-ß are complex and have not been elucidated in detail. IFN-ß binds to the type I IFN receptors INFAR-1 and INFAR-2. Its affinity to INFAR-2 is higher than to INFAR-1. This binding activates the JAK/-STAT (Janus kinases/signal transducer and activator of transcription proteins) signaling pathway leading to the expression of cellular genes (*e.g*., Mx genes, B2-microglobulin, 2'/5'-olygoadenylate synthetase and neopterin)[39]. Overall, the activation of signal--transduction pathways by IFN-ß leads to antiviral, immunomodulatory and antiproliferative effects [40]. Currently, IFN-ß is available as IFN-ß-1a or IFN-ß-1b. IFNß-1-a differs from IFN-ß-1b in the amino-acid sequence, tertiary structure and glycosylation status [41]. IFN-ß-1b was the first drug approved by the US Food and Drug Administration (FDA) for the treatment of MS in 1993.

Glatiramer acetate (GA), formerly known as copolymer-1 or Cop-1, is a mixture of random synthetic polypeptides composed of 4 amino acids (glutamate, lysine, alanine, and tyrosine) in a predefined molar ratio. GA's exact mode of action in MS is not completely understood, but extensive research has shown that GA, initially considered to be specific for MBP-related T cell immune responses, affects a variety of immune and non-immune pathways. It probably functions as an altered peptide ligand that promotes regulatory T cells instead of stimulating adverse T cell autoreactivity [42]. GA also modulates macrophages, microglia, and dendritic cells, and drives them into M2 phenotype and anti-inflammatory responses [43], [44], [45]. GA has also been shown to promote repair mechanisms, remyelination, and neurogenesis in the EAE model by augmenting the proliferation, migration, and differentiation of oligodendroglial and neuronal progenitor cells [46], [47]. In comparative trials with available interferons in RRMS, GA was as effective as IFN-β-1b [48]. GA's good safety profile has been established over many years of clinical use and its principal side effects include local-injection reaction. Although only moderately effective in reducing disease activity, GA is registered worldwide as a first-line platform therapy for patients with RRMS due to its long-term efficacy and safety reactions [31].

4. REMYELINATION ENHANCERS FOR THE TREATMENT OF MS

Myelin is fundamentally a lipid structure whose main components are cholesterol (40%) and glycosphingolipids (20%). While cholesterol allows the pods to be compacted, glycosphingolipids are necessary to form lipid rafts, facilitating communication with the cell and the extracellular matrix through its glycosylated residues [49], [50]. The synthesis of these compounds occurs in OLs and it is regulated by nuclear-receptor transcription factors. Both LXR and PPAR are members of the nuclear receptor superfamily that have a well-defined role in regulating lipid homeostasis and metabolic diseases. When LXR and PPAR are bound to the ligand, they form heterodimers with RXR and target genes that regulate the maturation of the OLs [50]. Sterol regulatory element (SREBP) is another transcription factor implicated in the synthesis of these compounds [51], whose expression is controlled by the PI3K-AKT1-mTOR signaling pathway in mammals [52]. There are additional highly conserved signaling cascades, such as the Wnt / β catenin pathway, the LINGO1 pathway and the Notch1 pathway [51], whose function is essential during myelin synthesis by preventing early differentiation of the OLs.

Table 2. Overview of main remyelination enhancers currently in clinical practice, under clinical trials or preclinical research.

Drug	Mode of Action	Currently in Clinical Practice / clinical Trials / Preclinical Research
Simvastatin	Inhibits HMG-CoA reductase. It stimulates the differentiation of OLs	Undergoing phase III clinical trials in SPMS; used as a treatment for hypercholesterolemia.
IRX 4202	RXR agonists They promote transcription of genes related to remyelination	Preclinical research
Retinoids		Undergoing phase III clinical trials; used as a treatment in dermatologic diseases and neoplasms.
Tamoxifen	They act on estrogen receptors stimulating myelin regeneration	Preclinical research; used for gynecological diseases.
Bazedoxifene		
Clobetasol	It acts on glucocorticoid receptor signaling in OPCs	Preclinical research; used for dermatologic diseases.
Benztropine	A muscarinic antagonist that inhibits Notch signaling and enhances remyelination	Preclinical research (with INFβ); used as a Parkinson's disease therapy.
Quercetin	Flavonoid that modulates Notch signaling in OPCs	Preclinical research
Indometacin	It acts on the Wnt/β catenin signaling pathway, leading OLs differentiation	Preclinical research; used as an analgesic and anti-inflammatory drug.
Biotin	Cofactor of acetyl-CoA carboxylases and other enzymes, leading to OLs maturation.	Undergoing phase III clinical trials.
Opicinumab	Monoclonal antibody against LINGO-1 (inhibitor of remyelination)	Undergoing phase II clinical trials.

Endogenous remyelination relies on oligodendrocyte progenitor cells (OPCs) function, which make up approximately 5-8% of cells in the adult brain. The remyelination process involves several events, such as the proliferation of the OPCs, their recruitment to the areas where the lesion is located, their differentiation towards mature OLs, and finally, the axon wrapping with new myelin sheaths [53]. Here, we summarize a list of remyelination enhancers for the treatment of MS. These compounds modulate OL function by promoting the differentiation of OPCs and the synthesis of lipids and proteins, or oppositely by blocking the signaling pathways which prevent differentiation of OLs. An overview of current myelin repair-related clinical trials is provided in Table **2**.

4.1. Compounds Promoting OL Differentiation and Remyelination

Simvastatin is a statin, a class of drug indicated for the treatment of hypercholesterolemia. It has been used in various trials to try to promote differentiation of OLs and myelin production. It inhibits HMG-CoA reductase, an enzyme implicated in the early stages of cholesterol biosynthesis, thus indirectly promoting the activation of SREBP and PPARγ, managing to stimulate the differentiation of OLs (through the synthesis of fatty acids) [54]. During the process of demyelinating diseases such as MS, the composition of myelin sheath can change, driving to myelin destabilization. For example, in the active phase of MS, there is an increase in circulating lipids, like cholesterol, the alteration of which has been associated with the disease progression [55].

Several pre-clinical trials obtained positive results using simvastatin for MS. This drug may modulate the neuroinflammatory response associated with MS and promote OLs differentiation and the myelination process by regulating lipid metabolism [56], [57]. In the experimental autoimmune encephalitis model of MS, simvastatin treatment was beneficial in reducing initial disease severity [58] and encouraging additional clinical trials. However, taken together, the results of these investigations shown great variability in the simvastatin effects [59-61]. Currently, based on these trials, a multicenter phase 3 study is ongoing. It will investigate the potential of simvastatin on MS progressive patients over a 3-year period.

Compound IRX 4202 and retinoids (such as 9-cis retinoic acid, an isomer of *vitamin A*) are RXR agonists [62, 63]. They are interesting candidates for promoting the transcription of genes related to remyelination due to their activity on nuclear receptors. On the other hand, estrogen receptors are other nuclear receptors that have been shown to participate in this remyelination process.

Tamoxifen and *Bazedoxifene* (EMA-approved drugs) also act on estrogen receptors, but certain studies have shown that Bazedoxifene could also activate independent mechanisms to accelerate the remyelination process [64]. Other selective estrogen receptor modulators appear to contribute to stimulating myelin regeneration.

Clobetasol acts on glucocorticoid receptor signaling in OPCs, inhibiting some enzymes involved in cholesterol biosynthesis and promoting their differentiation towards mature OLs. Furthermore, it exerts an important immunosuppressive effect, reducing the activation of T cells and decreasing the production of proinflammatory cytokines. This compound has been tested both in cell cultures of human OPCs and in animal models of MS, showing a great potential in promoting remyelination in patients [65].

4.2. Compounds which Block Signaling Pathways that Inhibit Remyelination

Benztropine is an FDA-approved muscarinic antagonist used for the treatment of Parkinson's disease. It blocks muscarinic receptors, thereby, in turn, inhibiting Notch signaling. Notch1 is a receptor found in OPCs and has two cut points for intracellular enzymes (the ADAM metalloprotease and the γ-secretase complex). The action of these enzymes causes the release of the intracellular NICD domain that is translocated to the nucleus, where it activates certain genes. It can interact with ligands like Jagged1 and Delta by inhibiting the differentiation of OPCs when these cells are in the early stages of differentiation. However, ligands like F3/contactin activate the non-canonical signaling cascade that promotes OPCs maturation [66]. Notch1 signaling pathway can be regulated exogenously by drugs such as benztropine. Also, it directly enhances remyelination, without affecting the immune system activity; however, some trials on animal models that had combined benztropine with immunomodulatory drugs, like INFβ or fingolimod, improved the remyelination process or revealed the possibility of reducing the immunosuppressor (fingolimod) doses to achieve the same efficacy. The combination of an immunosuppressive drug and a remyelination enhancer may have a significant effect on the development of new effective therapies for the treatment of MS [67].

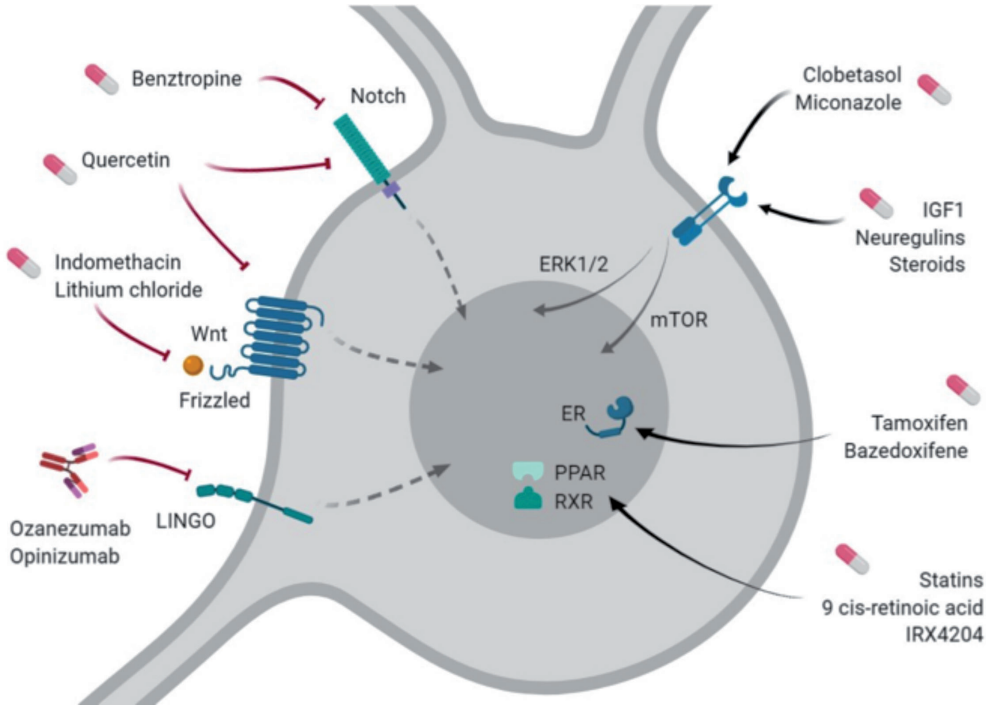

Fig. (1). Mechanism of action of the main drugs studied to promote remyelination by modifying lipid signaling. On the left side, signaling pathways that inhibit remyelination are represented (Notch1, Wnt / β catenin and LINGO1) by specific drugs. On the right side, cascades that promote the differentiation of OPCs and the synthesis of lipids and proteins (MAPK / ERK pathways, or nuclear receptors (RXR, PPAR or ER) and mTOR, respectively) are represented. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Compounds such as *quercetin*, a flavonoid that inhibits γ-secretase, are also interesting since they modulate Notch receptor responses, favoring remyelination [62].

Indometacin is a non-steroidal anti-inflammatory drug that acts on the Wnt/β catenin signaling pathway. This pathway is activated when Wnt proteins bind to Frizzled receptors. This leads to intracellular signaling and arrival of β catenin to the nucleus, where it stimulates the transcription of genes that prevent the exit of the cell cycle of the OPCs and stop their differentiation. In remyelination after injury, this pathway is necessary to generate enough OPCs, but should then be switched off so that myelin-producing OLs can be differentiated [68]. Indomethacin could promote remyelination in MS patients, because it is able to cross the blood-brain barrier and act on OPCs, stimulating their differentiation. Several *in vitro* studies have confirmed this effect of Indometacin. Despite the well-known safety profile of this drug, translation of this knowledge to the clinic still requires preclinical and clinical studies [69].

Opicinumab is a human monoclonal antibody against LINGO-1. It is a glycoprotein localized in the extracellular domain of the Nogo receptor that is selectively expressed in the CNS, both in oligodendrocytes and neurons. Certain pathologies and CNS injury, including multiple sclerosis lesions, can cause overexpression of this protein [70]. LINGO-1 negatively regulates OL differentiation and therefore remyelination, suggesting that the inhibition of LINGO-1 function by Opicinumab may represent a promising therapeutic approach to the treatment of MS. This antibody enhances axonal myelination *in vitro* and endogenous remyelination in several animal models through encouraging differentiation of OPCs [71]. Opicinumab has been shown to be safe and effective in phase 1 trials in MS patients and healthy controls [72]. Furthermore, a phase 2 study was performed to investigate the clinical safety, efficacy, and pharmacokinetics of four different doses of opicinumab versus placebo in relapsing MS patients. Nevertheless, findings did not show a significant dose-linear improvement in the disability of MS patients compared with placebo [73]. Additional studies are required to investigate whether some subpopulations identified in the study might benefit from opicinumab treatment at an optimum dose.

5. VITAMINS, AMINOACIDS AND FATTY ACIDS AS ANTI-INFLAMMATORY AND RE-MYELINITATING MOLECULES

The role of *vitamin D* in MS has been recently reviewed [4], supporting its role in the onset and progression of MS. Remarkably, vitamin D has been demonstrated to interact with a variety of other risk factors, from genetic predictors like HLA-DR1 genotype to behavioural factors like smoking.

Biotin (vitamin H) appears to have a significant effect on remyelination. This molecule acts as a cofactor for several essential enzymes, such as acetyl-CoA carboxylases, the limiting enzymes in the synthesis of malonyl-CoA. Malonyl-CoA is the basis for the fatty acids synthesis in the brain. In addition, it coordinates the balance between fatty acids synthesis and oxidation. It has been proposed that high doses of biotin increase the synthesis of fatty acids required for remyelination. Furthermore, biotin acts as a coenzyme of additional carboxylases involved in the metabolism of pyruvate and amino acids in neurons. These enzymes produce key intermediates of the tricarboxylic acid cycle and therefore, high doses of biotin could increase ATP production in demyelinated neurons, reducing the dysfunction that occurs [2].

GEMSP is an emerging novel therapeutic compound for MS, according to recently reported beneficial effects in pre-clinical and clinical studies. It consists of a mixture of functional polypeptides: fatty acids, antioxidants, free radical scavengers and amino acids linked individually to poly-L-Lysine (PL) [74]. Molecular analyses also showed that GEMSP preserves myelin integrity [75]. In an open clinical trial in humans with 193 patients with MS, EDSS value was significantly lower than in the control group and the health improvement of MS group compared with control group was 24% higher [76]. Additional studies have shown that an increase in the administration of polyunsaturated n-3 AG (PUFAs) in neurodegenerative diseases has beneficial effects due to its neuroprotective and anti-inflammatory effect [77] Fig. (**1**).

CONCLUSION

Multiple sclerosis (MS) is a high-frequency neurological disorder in young adults. Although there are some genetic and environmental factors that have been related to the onset of the disease, these are not still completely well understood and nowadays MS can neither be prevented nor its symptoms can effectively be treated due to disease heterogeneity. For this reason, the search for prognostic factors and also effective treatments for MS has long aroused among clinicians and researchers. Immunomodulatory therapies that currently exist have proven limited success, mainly because these therapies only delay disease progression [31]. Although recent advances in the genetics of MS will contribute to the discovery of new drugs [12], the development of treatments that promote endogenous remyelination is essential to reverse MS-related impairments. Different therapeutic strategies focused on the activity modulation of OL-specific signaling pathways have been tested in order to allow the promotion of endogenous remyelination. In OL cells, there are several metabolic cascades (such as lipid synthesis) that affect the expression of genes involved in the remyelination process. Currently, numerous compounds are being studied with promising effects on remyelination. Some of these compounds (*e.g*. Bazedoxifene) are already approved drugs for other pathologies, which facilitate and simplify safety and tolerance studies. Others are novel compounds, such as monoclonal antibodies, that require further investigation before they can be used in the clinic. Remarkably, several studies have highlighted that exogenous administration of specific lipids and peptides, such as GEMSP, or vitamins, such as biotin, can promote myelin synthesis more effectively while promoting recovery of MS cognitive and motor impairments. This field of study could be of potential interest when establishing diets rich in certain foods that stimulate remyelination. Although all of these possible remyelinating drugs may have advantages over the currently available immunomodulatory treatments due to their milder side effects, more research on these compounds is still needed in order to better characterize their effects in clinical trials and also the interaction with additional drugs. In summary, we anticipate that in the next few years, new treatment options will be available for patients with MS. Due to disease complexity, these therapies will combine immunosuppressive drugs for treatment options to stop the progression of the disease with a well-tolerated safety profile, remyelinating enhancers for promoting central nervous system remyelination and pharmacological interventions related to neuropathic pain in order to provide effective treatments on initiation and progression of MS.

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