Novel Treatments for Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by demyelination of the axons in the brain and spinal cord. MS affects approximately 400, 000 people in the United States alone. Although this is an acquired disease there is no cure. Current treatment options focus on managing MS symptoms and slowing the progression of the disease. In this review article, we examine new treatment modalities, ozanimod, siponimod, and leukemia inhibitory factor nanoparticle (LIF-NP). Ozanimod, an S1P modulator, was shown to be more effective in reducing annualized relapse rates, T2 MRI brain lesions, and T1 gadolinium-enhanced MRI lesions compared to the traditional IFβ-1a treatment option when treating relapsing-remitting multiple sclerosis. Siponimod, also an S1P modulator, produced a reduction in confirmed disability progression when treating secondary progressive multiple sclerosis. The LIF-NP, a recent discovery by Cambridge scientists, has the potential to not only slow the progression of the MS but promote neuronal protection and remyelination in the central nervous system. This discovery could lead to a possible cure for MS. These treatments for MS aim to provide patients with the ability to delay disease progression and possibly completely resolve all symptoms.

Introduction

Multiple sclerosis (MS) is an immune-mediated disease that causes damage to the central nervous system (CNS) as a result of demyelination thus leading to neurodegenerative deterioration (1, 2). MS affects approximately 2.3 million people worldwide and is the leading cause of disability in young adults in the U.S. (1, 3). The symptoms observed in patients with MS are due to the disruption of the myelinated axons tracts in the CNS (4). The most prevalent symptoms include fatigue, weakness, vision problems, spasticity, gait difficulties, and numbness and tingling all over the body (2, 4). As MS progresses patients may also experience memory loss, slower information processing, depression, and bladder and bowel dysfunction (2, 4). The wide range of symptoms seen in patients with MS reflects multifocal lesions in their CNS (4).

Although there is extensive ongoing research to better understand the pathogenesis of MS, scientists have been unable to confirm its cause. What scientists do know is that environmental and genetic factors play a role (1, 4). Researchers have determined that the inflammatory aspect of MS is controlled primarily by immune cells including CD8+, CD4+, and Th17 T cells (1–3, 5, 6). When T cells attack myelin, they trigger an immune response that involves cytokine secretion. The cytokine secretion activates an inflammatory cascade that recruits other immune cells that cause further inflammation and degradation which leads to neuroinflammation and axonal damage (1–3, 5, 6). B cells also play a role in MS inflammation by producing antibodies against myelin that phagocytose myelin and oligodendrocytes (1, 3, 5). This immune response that takes place in the CNS causes an increase in the permeability of the blood-brain barrier (BBB) allowing the movement of more immune cells toward the axons of the CNS resulting in the formation of sclerotic plaques or lesions, demyelination, and neurodegeneration (3, 6).

There is no definitive diagnostic test for MS. Diagnosing MS relies on clinical presentation, neuroimaging, and cerebrospinal fluid (CSF) analysis. Clinicians look for manifestations of signs and symptoms of MS while ruling out other conditions that may resemble MS (4, 6). An MRI scan is a critical tool in diagnosing MS and determining the progression of the disease (4, 6). Newer MRI techniques are able to detect both white and gray matter damage in the CNS (4). MRI scans can also be used to detect MS lesions that appear throughout the CNS. These lesions are most easily recognized in the white matter as focal areas of demyelination and inflammation (7). There are four major classifications of MS include relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS) (6).

This review article examines three novel treatments for MS ozanimod, siponimod, and LIF-NP — and offers insight into which of these is most promising as an effective MS therapy.

Methods

The database used to collect articles for this paper was PubMed. PubMed was used because it is publicly available and contains important biomedical research. The initial search criteria were the keywords “multiple sclerosis.” This initial result provided over 90,000 articles. Because we were looking for new treatments, we narrowed down the result by excluding any articles prior to 2018 and due to the scarcity of MS in children, any articles involving children. A number of the background articles were located in the reference list of relevant articles. While gathering background information, we noticed an increase in IL-6 for patients affected by MS and proceeded to look for any treatments that affected that biological pathway. In order to see developing treatments, we filtered the results using a randomized clinical trial as inclusion criteria as well as IL-6 modifiers. The data in the articles were analyzed based on the type of MS that was treated and if the new therapies were compared to current treatments or placebo groups.

Discussion

Current treatment modalities for MS

Since there is no cure for MS, current treatment options only slow the progression of the disease and help manage the associated symptoms. The different types of therapeutic

treatments for MS include injectables, oral administrations, and infusions (IV) (5, 6). There are now 14 medications that have been approved by various regulatory agencies around the world to treat MS (6). Some of them include interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, ocrelizumab, and mitoxantrone (8). The majority of these treatments are used to help stop the body's immune attack on the myelin sheath, thus limiting the relapse rate (3, 5, 6). While the bulk of MS treatments do help to repress the immune attack on the myelin they also suppress the body's immune system leaving patients vulnerable to illness and infection (3, 6). In the realm of treatment options for MS, there is an unmet need to provide neuroprotection while also repairing previously damaged nerve fibers.

Ozanimod

RRMS is the most prevalent type of MS. It is characterized by attacks of worsening neurological function called relapses that are followed by partial or complete remission (10, 11). Approximately 85% of individuals who are initially diagnosed with MS present with RRMS (10, 11). While complete physical recovery from a relapse can occur, about half of all relapses are associated with lingering neurological deficits resulting in a persistent increase in disability (11). Even though there is currently no cure for MS, treatment options do exist for RRMS.

One novel drug to treat RRMS is known as ozanimod (Zeposia®). Ozanimod is a sphingosine 1-phosphate (S1P) receptor antagonist. S1P is a phospholipid involved in lymphocyte migration and other physiological processes (9). Ozanimod selectively binds to 2 of the 5 S1P receptors: $S1PR_1$ and $S1PR_5$ (1, 3). Functional antagonism of $S1PR_1$ inhibits the release of immune cells such as B cells and T cells from lymph nodes, thereby reducing the number of lymphocytes in the peripheral blood (9, 11). The modulation mechanism of $S1PR_5$ is not known, but it may involve the reduction of lymphocyte migration into the CNS, thus being neuroprotective (9, 11). Currently, ozanimod is under review by the U.S. Food and Drug Administration (FDA) for the treatment of RRMS. The clinical efficacy, safety, and tolerability of ozanimod for the treatment of patients with RRMS have been demonstrated in the Phase III RADIANCE and SUNBEAM clinical trials (11).

The RADIANCE and SUNBEAM trails were both multicenter, randomized, double-blind, double-dummy, active-controlled trials evaluating the efficacy, safety, and tolerability of two doses of oral ozanimod (0.5 mg and 1 mg) versus interferon-beta-1a (Avonex®), a modestly efficacious weekly RRMS intramuscular treatment (12). Interferon-beta-1a (IFβ-1a) is a cytokine that modulates the immune system by reducing antigen presentation and T-cell proliferation (13). The RADIANCE clinical trial was conducted over a 24-month treatment period and included 1,320 people living with RRMS; the SUNBEAM trial was conducted over a 12-month treatment period that included 1,346 people living with RRMS (10). The goals of both trials were to assess annualize relapse rates (ARR) during the treatment period and evaluate the number of new or enlarged hyperintense T2-weighted brain MRI lesions, the number of gadolinium-enhanced brain MRI lesions and the percent change from baseline in brain volume (10, 12).

In the SUNBEAM trial, the researchers found a significant decrease in ARR for ozanimod 0.5 mg (ARR = 0.24; $p = 0.0013$) and 1 mg (ARR = 0.18; $p < 0.0001$) compared to IFβ-1a (Avonex) (ARR = 0.35). They also saw a significant reduction in new or enlarging T2 lesions for ozanimod 0.5 mg (25%; $p = 0.0032$) and 1 mg (48%; $p < 0.0001$) compared to IFβ-1a. There was also a decrease in gadolinium-enhanced MRI lesions for ozanimod 0.5 mg (34%; $p = 0.0182$) and 1 mg (63%; $p <0.0001$) compared to IFβ-1a (12).

Results from the RADIANCE trial were very similar to those observed in the SUNBEAM trial. A significant decrease in ARR for ozanimod 0.5 mg (ARR = 0.22; $p = 0.0167$) and for 1 mg (ARR= 0.17; $p < 0.0001$) compared to IFβ-1a (ARR = 0.28) was observed. They also found a significant reduction in new or enlarging T2 lesions for ozanimod 0.5 mg (34%; $p = 0.0001$) and for 1 mg (42%; $p < 0.0001$) compared to IFβ-1a. In addition, there was also a significant decrease in gadolinium-enhanced MRI lesions for ozanimod 0.5 mg (47%; $p = 0.0030$) and for 1 mg (53%; $p = 0.0006$) compared to IFβ-1a (12).

Both clinical trials demonstrated ozanimod to be more effective than IFβ-1a in treating patients with RRMS. These results can be explained by the processing rates of the two drugs. According to a post hoc analysis, ozanimod was metabolized quicker than IFβ-1a (14). Therefore, since ozanimod can be processed faster in the body, it is able to work sooner than IFβ-1a.

In addition to being effective, ozanimod was well tolerated by most participants. However, there were a few participants who suffered from adverse effects (AE). About 4.9% of participants experienced an increase in alanine aminotransferase (ALT) that was above three times the upper limit of normal. Most of the participants with elevated ALT levels did not require discontinuation of ozanimod (9). A total of 12 participants reported experiencing ≥1 serious AE. Two serious AE that were reported in these studies were pancytopenia, low counts for all three types of blood cells, and acute myocardial infarction. No serious AE occurred in more than one participant, for that reason researchers do not consider them related to ozanimod. (9).

In a separate study, researchers compared the safety and efficacy of ozanimod to fingolimod by using patient data from the ozanimod RADIANCE and SUNBEAM trials, and the fingolimod FREEDOMS trials (11). Fingolimod was the first oral disease-modifying therapy approved for the treatment of RRMS, and like ozanimod, it is an S1P receptor modulator. Unlike ozanimod, fingolimod binds to 4 of the 5 S1P receptors: $S1PR_1$, $S1PR_3$, $S1PR_4$, $S1PR_5$ (9, 11).

The results of this study showed that ozanimod and fingolimod were comparable in terms of efficacy outcomes on the ARR and confirmed disability progression, but ozanimod was associated with a significantly lower risk of any AE (3). In the first-year outcomes, ozanimod had higher absolute mean lymphocyte count (difference in means: 0.4 × 109/l) and lower risk of ALT elevations compared to fingolimod (11). In the second-year outcomes, ozanimod had significantly lower risks of AE leading to discontinuation, herpetic infection, basal cell carcinoma, bradycardia, and ALT elevations compared to fingolimod (all $p < 0.05$) (11). One possible reason why ozanimod was associated with a significantly lower risk of any AE is due to the fact that ozanimod is more selective than its

predecessor, fingolimod. As previously stated, ozanimod binds to $S1PR_1$ and $S1PR_5$, whereas, fingolimod binds to $S1PR_1$, $S1PR_3$, $S1PR_4$, $S1PR_5$. The lack of selectivity for fingolimod may be the reason why there are more AE associated with it.

Ozanimod has shown great promise as a relapsing multiple sclerosis treatment through the trails previously mentioned. In the RADIANCE and SUNBEAM trials, ozanimod showed to be an effective drug by demonstrating significant reductions in ARR, in new and enlarging T2 lesions, and in gadolinium-enhanced MRI lesions (12). In the comparative study with fingolimod, ozanimod proved to be associated with a more favorable benefit-risk profile than fingolimod when considering the cardiac monitoring, safety outcomes, and efficacy outcomes (11). Based on this information, ozanimod has the potential to provide RRMS patients and their physicians an additional option for treating relapsing multiple sclerosis (11).

Siponimod

Another drug in the same family as ozanimod is siponimod. This drug, by Novartis Pharmaceuticals, is also a selective modulator for the $S1PR_1$ and $S1PR_5$ receptors (7, 15). Additional research has found that these S1P receptors are located abundantly on lymphocytes, oligodendrocytes, astrocytes, and erythrocytes (7). Siponimod is indicated for the treatment of SPMS. SPMS is a form of MS that progresses from RRMS, despite being treated (16). Siponimod is a lipophilic drug that can cross the blood-brain barrier, making it a viable drug to decrease the inflammation that could occur from the disease. Ginatile et al. investigated this potential benefit using mice that had experimental autoimmune encephalitis (EAE) and injecting the drug directly into the CSF. Their results demonstrated a dose-dependent effect, with a high dose of 4.5 mg/day completely inhibiting EAE. A lower dose of 0.45 mg/day improved disease severity (7). This study also noted a significant reduction in astrogliosis, which is an increase in the number of astrocytes resulting from the loss of nearby neurons from the CNS due to trauma or disease, and an increase in gamma-aminobutyric acid (GABA) signal in the striatum of siponimod-treated mice (7). When it comes to treating neuroinflammation, siponimod was shown to decrease oligodendrocyte and axonal loss (7). This suggests that it might be able to protect axons during both the acute and the chronic demyelinating phases of MS (7). These studies are important because even a minor change in expanded disability status scale (EDSS) for patients with SPMS, has a significant change in brain function and daily activities (15). EDSS is a scale to evaluate disability in MS and monitoring changes in the level of disability over time which range. The scale ranges from zero to 10 in 0.5 increments.

Siponimod's primary function was analyzed in a double-blind phase-III clinical trial by Kappos et al. which evaluated the effectiveness and safety of the drug in patients suffering from SPMS. The inclusion criteria were patients who were 18 to 60 years old who had a diagnosis of SPMS and documented moderate-to-advanced disability indicated by an EDSS score of 3.0 to 6.5 at screening, a history of RRMS, documented EDSS progression in the 2 years before the study. Eligible participants also had to have no evidence of relapse in the 3 months before randomization (15). The participants were randomized in a 2:1 manner, with the experimental groups receiving 2 mg of siponimod or a placebo. A full neurological assessment was initiated at baseline to assess walking range, functional systems, and an EDSS score. This assessment was done every 3 months. MRI scans were also part of the assessment and were taken 12, 24, and 36 months from baseline. The primary endpoint was the start of the study to 3-month confirmed disability progression (CDP). CDP is defined as a 1-point increase in EDSS if the baseline score was 3.0 to 5.0, or a 0.5-point increase if the baseline score was 5.5 to 6.5, which would be confirmed at a visit at least 3 months later. The study also analyzed the data looking for secondary endpoints. These included the time to 3 months where the patient had a 20% decrease from baseline, when performing the 25-foot walk test (T25FW), ARR, and a change in T2 lesion volume.

There was a total of 1,651 patients randomly assigned — 1,105 to the siponimod group and 546 to the placebo group. The duration of the study had a median time of 21 months with exposure to the study drug at 18 months (15). The characteristics of each group were similar. The study results showed 26% of the siponimod group versus 32% of the placebo had a 3-month CDP, with a hazard ratio of 0.79 which demonstrated a risk reduction of 21%, with a p-value of 0.0131. When the data is divided into smaller subgroups, the results favor siponimod over the placebo. Evaluation of CDP done at 6 months showed a reduction by siponimod with a hazard ratio of 0.74. This translated to a 26% risk reduction with a p-value of less than 0.05. ARR was decreased with siponimod when compared with placebo, from baseline to confirmed first relapse, with a risk reduction of 46% with a p-value of less than 0.0001 (HR=0.54). Lesion volume when compared to baseline, was lower with siponimod than with placebo, with a group difference of -695.3 mm3 and a p-value of less than 0.001. Brain volume decreased at a lower rate with siponimod than with placebo. Unfortunately, there wasn't any significant reduction in time to 3 months where the patient had a 20% reduction from baseline when performing the T25FW for the entire population of the study.

Even though the clinical benefits of using siponimod are apparent, there are also AE. The highest frequency of AE includes headache, nasopharyngitis, urinary tract infection, and falls, which were reported in more than 10% of patients in both treatment groups (15). The more serious AE affected a low percentage of the population in the treatment groups. These included increased liver transaminase concentrations, basal cell carcinoma, concussion, depression, urinary tract infection, suicide attempts, gait disturbances, multiple sclerosis relapse, and paraparesis. There were also 4 deaths for each treatment group caused by metastatic gastrointestinal melanoma within 4 months of using siponimod. Patients who were in the siponimod treatment groups had a slight increase, proportionally, in adverse effect than the placebo group. This is due to the immune modulation of the drug. Siponimod also has an adverse effect on the cardiovascular system due to its mechanism of action. In comparison patients receiving this S1P modulation were more proportionally affected by bradycardia, hypertension, lymphopenia, and macular edema at the start of treatment. Convulsions were also more common with siponimod than with placebo.

Summarily, the EXPAND clinical trial has shown a sizable reduction in 3-month CDP compared with placebo. This means

it can be used as an effective disease-modifying treatment with those suffering from SPMS.

LIFnano

Scientists at Cambridge University have discovered a promising regenerative treatment known as leukemia inhibitory factor (LIF). LIF is a stem cell growth factor that has the potential to slow the progression of MS while also repairing damage to the CNS seen in diseases like MS (18). LIF is a four-helix bundle protein and is a part of the IL-6 cytokine family expressed in the hypothalamus and anterior pituitary (18–20). It has been shown to promote neuroprotection while also possessing therapeutic benefits for treating MS (18).

LIF is known to act on cell surface receptors, gp190, and has anti-inflammatory effects (Figure 1). Interleukin-6 (IL-6), a pro-inflammatory cytokine suppresses the transcription of the LIF receptor (18, 19). This suppression makes the cells unable to contact LIF; this, in theory, suppresses the anti-inflammatory processes of LIF (18). IL-6 is shown to be elevated in the plasma of patients with MS (19). LIF is naturally occurring in the CNS and also required for myelination and remyelination (18). LIF-knockout mice have been shown to have a delay during development (22). It has been recognized that LIF regulates the lineage of regulatory T cells. This is vital in treating MS because MS is known to be a T-cell-mediated autoimmune disease. LIF has also recently been discovered to be a pro-myelination factor (22).

Despite all of its benefits, LIF has a short half-life (20 minutes). LIF's rapid degradation *in vivo* warranted further research as a potentially effective treatment for MS (18). Researchers used nanoparticles to overcome the short half-life of LIF and determine whether it could be effectively delivered to the CNS. Nanoparticles provide a sustained-release delivery system through the blood-brain barrier and are proven to be biodegradable and biocompatible (18, 19).

The nanoparticles were used to target the delivery of LIF to oligodendrocyte precursor cells (OPC) within the brain. OPCs help areas of damage and promote differentiation into mature oligodendrocytes which then are able to repair myelin (22).

Researchers conducted an experiment to identify if improved OPC biological function was due to the signaling induced by LIF-nanoparticle (LIF-NP) treatment. *In vivo*, the goal was to demonstrate OPCs to survival, proliferation, and differentiation for remyelination to occur (22). Researchers assigned six treatment groups, Group 1: untreated controls,

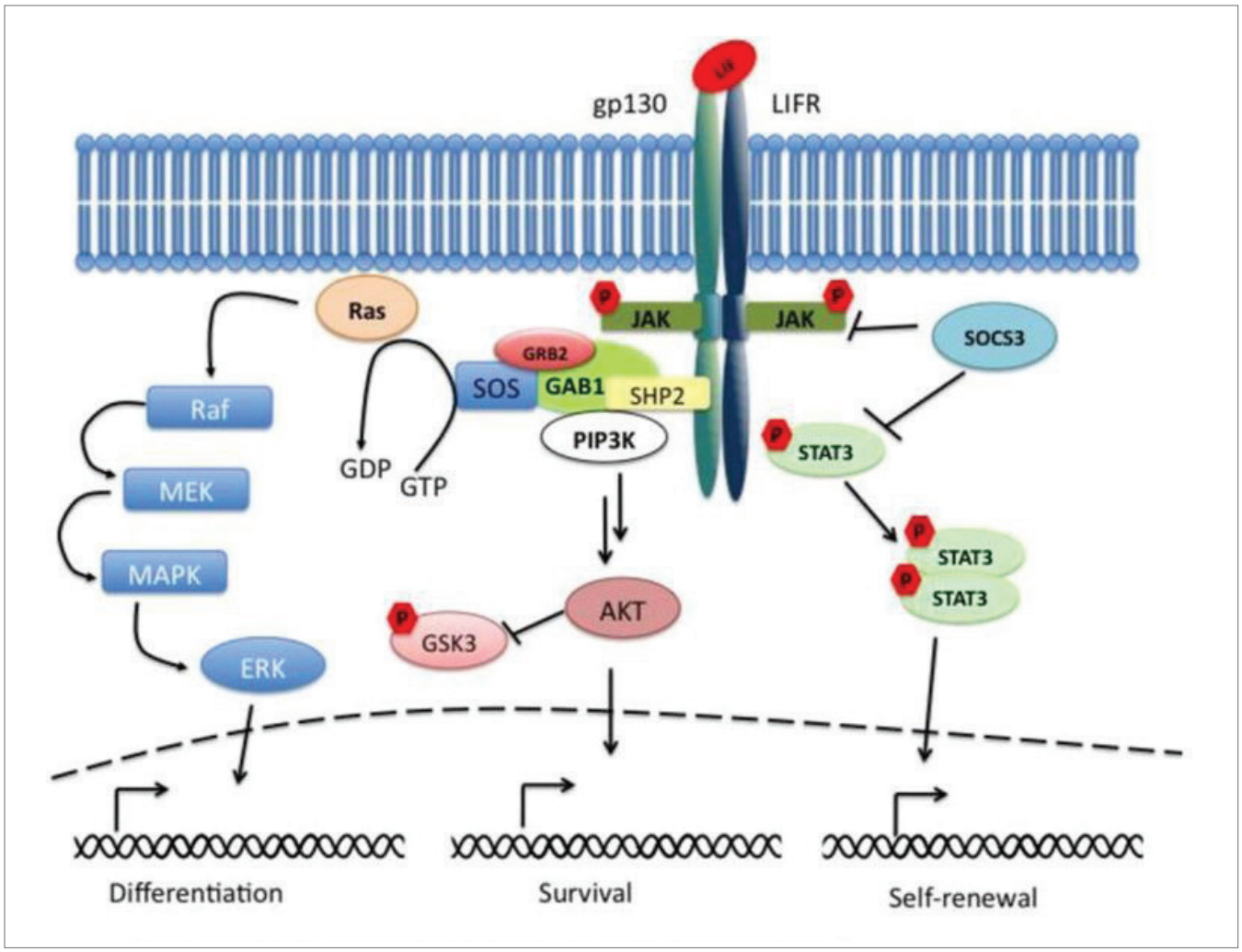

Figure 1. Schematic of the leukemia inhibitory factor (LIF) pathway (20).

Group 2: recombinant LIF (positive control) (100 U/ml), Group 3: NG2- targeted LIF-NP (300 mg/ml), Group 4: non-targeted LIF-NP (300 mg/ml), Group 5: NG2-targeted empty-NP (300 mg/ml), Group 6: non-targeted empty-NP (300 mg/ml). LIF-NP treatment was given to each group and survival and proliferation were measured after being treated for 24 hours. Myelin basic protein (MBP) was assessed for differentiation, and the results showed increased MBP in the group treated with NG2-targeted LIF-NP (19). The group that received the NG2-targeted LIF-NP treatment was seen to have a significantly greater number of myelin basic proteins and also oligodendrocytes compared to the targeted empty-NP group. This solidifies the requirement for LIF delivery and targeting specific NG2 cells to accomplish enhanced OPC maturation (19).

The next step was to examine the LIF-NP *in vivo*. Myelin toxin lysophosphatidylcholine (LPC) was injected into the corpus callosum of mice to simulate a model of CNS demyelination. The three treatment groups for the in vivo study consisted of, NG2-targeted LIF-NP, non-targeted LIF-NP, NG2-targeted empty-NP. The mice were then injected with the LIF-NP in the exact same location 8 days following the LPC injection. Remyelination in the mice was then examined by electron microscopy 10 and 17 days following the LIF-NP treatment. The electron micrographs show increased remyelination in mice treated with targeted LIF-NP compared to non-targeted LIF-NP and the targeted empty-NP.

It was identified that the group that received NG2-targeted LIF-NP had the highest percentage of myelinated fibers and the lowest mean G ratio. This indicated the NG2-targeted treatment group had the thickest myelin and also the thickest axon diameter when compared to the other groups. There were no AE observed in any of the treated mice. This study confirmed that *in vitro* NG2-targeted LIF-NP were able to bind to OPCs and promote differentiation, while *in vivo* the NG2-targeted LIF-NP improved remyelination within the CNS (22). This research revealed how LIF-NP can contribute to neuroprotection while also remyelinating within the CNS. This technology will hopefully be able to halt the neuro-axonal damage while also promoting remyelination in the CNS. Clinical trials with this therapeutic technology will begin in 2020 (18).

Discussion

As of today, MS remains one of the most prevalent debilitating diseases seen in young adults. Current pharmacotherapies on the market for treating MS focus on slowing down the progression of the disease while only managing symptoms.

Ozanimod is an S1P modulator that has shown to be effective in reducing ARR, while also decreasing the size of T2 MRI brain lesions and T1 gadolinium-enhanced MRI lesions when compared to the traditional IFβ-1a treatment options. Siponimod, also an S1P modulator, was proven to be an effective treatment for SPMS. These results show that ozanimod was better at reducing the disease progression when compared to IFβ-1a, which is an approved treatment for RRMS. The AE profile of ozanimod is similar to currently approved treatments on the market. As of March 2020, ozanimod has been FDA approved for the treatment of multiple forms of relapsing MS.

Patients treated with siponimod showed a larger reduction in CDP. This study is important, because this drug has consistently proven to reduce CDP in SPMS patients. This reduction corresponds to small changes in EDSS which can present as significant changes in neurological functions and day-to-day activities. When comparing siponimod with other S1P receptor modulators, like fingolimod, the safety profile is similar and produces less bradycardia. Patients that use this drug should be under medical supervision until the bradycardia is gone, which occurs after about 7 days. This study corrected this with a dose titration but if this adverse effect could be rectified, siponimod can be very beneficial to slow the progression of SPMS. This study could have tested patients who have relapsed recently and determine if the drug has any effect on active SPMS. The duration of the study was not long enough to determine long term AE associated with continued drug use. Siponimod should be evaluated for how selective it is for $S1PR_1$ and $S1PR_5$ and if genetics play a role in its metabolism. With these AE, siponimod has currently been approved for the treatment of SPMS in both the European Union and the U.S. Ozanimod and siponimod demonstrated success in slowing the progression of the disease with less frequent AE when compared to current MS treatment options. These drugs did not reverse the damage already caused by MS.

LIF-NP has been proven safe and effective in animal models of MS. Since LIF-NP uses a molecule that is naturally occurring in the human body, the presence of AE is very limited compared to other MS treatment options. LIF-NP not only displayed neuroprotective activity in the CNS but it also assisted in the repair and remyelination of axons by promoting the differentiation of OPCs. This suggests that LIF-NP can prevent the progression of neurodegenerative diseases like MS while also promoting tissue repair in previously damaged areas of the CNS. While further clinical research is needed to be conducted in humans to test for safety and efficacy, the promising data seen in the animal models show that LIF-NP has the potential to be a curative treatment for MS.

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