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Editorial

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Remyelination in Multiple Sclerosis: A Focus on Anti-LINGO-1 (Opicinumab)

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Editorial

Remyelination, the process of creating or restoring function to the myelin-forming oligodendrocytes, has been the latest development in the arsenal of Multiple Sclerosis (MS) therapies. Many of the current treatments For Central Nervous System (CNS) demyelinating diseases are immune-modulating in hopes to stop the progression of disease and reduce further damage. MS, the most prevalent CNS demyelinating disease in the United States, is a chronic disease of inflammatory demyelination and neurodegeneration of axons in the CNS. Extensive research is being performed in laboratories and clinical centers to elucidate repair mechanisms to damaged neurons. The harvest of this impressive research has identified several therapeutic targets to be upregulated in animal models and humans of CNS disease, one specific example is a CNS-specific membrane-associated glycoprotein called LINGO-1(leucine-rich repeat and Ig domain-containing, Nogo receptor interacting protein) [1,2]. LINGO-1 is selectively expressed in oligodendrocytes and neurons of the CNS and functions as a negative regulator of oligodendrocyte differentiation, myelination, neuronal survival, and axon regeneration [3,4]. The function and selectivity of LINGO-1 makes it an ideal target to block in treatments for demyelinating diseases.

Opicinumab (also known as BIIB033) is a human, anti-LINGO-1 IgG1 antagonist monoclonal antibody created to restore function to oligodendrocytes and remyelinate damage neurons in patients with MS. Phase 1 trials published in August 2014 reported no serious adverse events to administration of anti-LINGO-1 and was well-tolerated in patients with relapsing-remitting MS, secondary progressive MS, and healthy volunteers [5]. Two Phase 2 trials, RENEW and SYNERGY, were later conducted to assess the clinical potential of opicinumab in CNS demyelinating diseases. RENEW was a proof-of-concept study to illuminate the safety, tolerability, and efficacy of opicinumab treatment for 32 weeks in patients with acute optic neuritis [6]. The improvement in optic nerve conduction was not as apparent at first examination, measured as recovery of affected optic nerve conduction latency, in the intention-to-treat analysis. The study showed no significant difference between the opicinumab group and placebo; however, the prespecified per-protocol analysis did present possible improvement in the opicinumab group at week 32. The authors further explained RENEW gave insight into the rapid progression of disease after onset of acute optic neuritis as 90% of patients showed delay of full-field visual-evoked potential in affected eye before initiation of treatment. The group, and medical community, suggested further investigation as enhancement of remyelination with opicinumab may be possible in a subgroup of patients.

The most recent reports in anti-LINGO-1 research was delivered June 2016 reporting opicinumab unfortunately missed the primary endpoint in the Phase 2 clinical trial SYNERGY [7]. The endpoint included measurements of physical function, cognitive function, and disability in 418 patients with Relapsing Forms of MS (RMS). Four experimental groups included separate dosing (3, 10, 30, 100mg/kg) once every 4 weeks intravenous infusions up to week 72 with interferon beta-1a once-weekly intramuscular injections up to week 84. Although the primary endpoint was not met, some interesting discoveries were made into dosing and efficacy of opicinumab. An inverted U-shaped dose response was identified with more favorable outcomes at the 10 and 30mg/kg dose. Subgroup analysis also showed that treatment was more effective in younger patients and those with shorter disease duration. The authors concluded that based on some of the positive findings from SYNERGY, additional studies with opicinumab are warranted with appropriate adjustments to the clinical study design. The SYNERGY trial was a breakthrough study because it showed

improvements are possible in RMS with the addition of remyelination therapy. Patients on highly effective treatments for MS such as natalizumab, fingolimod, or dimethyl fumarate, were specifically excluded from this trial, which opens the door to further combination drug trials. A future clinical trial is currently in the scheduling process and will be using the intermediate dose 10mg/kg of opicinumab as an add-on to these established MS immune therapies. There is hope that this additional research will provide highly anticipated data into the ability to enhance myelination and axonal regeneration in RMS through anti-LINGO-1. The current state of MS research is a sight to behold. Exponential improvements in therapies and new drug discoveries occurring annually, allowing clinicians to anticipate implementing additional treatments in their practice. Opicinumab as an add-on or standalone therapy is still to be determined. Furthermore, the balance of silencing the inflammatory process in MS while stimulating remyelination through a combination of immune-modulating and remyelinating therapies is unclear at this moment. However, each trial provides a clearer picture in understanding MS progression and treatment. The phase 2 trials with opicinumab have provided hope to regain lost myelin and promising improvements for MS patients in the near future.

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