Remyelination therapy goes to trial for multiple sclerosis

Pedro Brugarolas, PhD
Brian Popko, PhD

Correspondence to: bpopko@uchicago.edu

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With a number of new drugs approved, the last decade has seen tremendous progress in the treatment of multiple sclerosis (MS). All current drugs work by decreasing inflammation through modulation of the immune system, and while they have been very efficient in reducing the rate of relapses, their impact on the chronic disease course is unknown. A current thought in the MS therapeutics community is that drugs that enhance remyelination may be more effective in reducing long-term disability. This hypothesis is based on the observation that disability in MS increases with age as the capacity of oligodendrocytes to remyelinate decreases.1 Additional support for this hypothesis comes from extensive preclinical studies showing that promoting remyelination either by transplanting myelinating stem cells2,3 or by pharmacologic enhancement of endogenous myelination processes reduces clinical severity in animal models of MS.4,5 In this issue of Neurology® Neuroimmunology & Neuroinflammation, Tran et al.6 take this possibility to its exciting next step by reporting the results of the phase I clinical trial of the first drug aimed at promoting myelin repair.

The drug under study is a monoclonal antibody named BIIB033. Monoclonal antibodies are becoming very popular therapeutic agents due to their high affinity and specificity to their target, which results in safe and selective treatments. In addition, their advantageous patent protection compared to traditional drugs and their straightforward (although expensive) development process make these novel therapeutics much coveted by pharmaceutical companies. In the current article, the authors report that the drug under study is safe and the rate of adverse events low, which is the main goal of phase I trials. These timely results are important for physicians and patients considering enrolling in the already-ongoing phase II trial.

BIIB033 targets LINGO-1, a protein expressed in oligodendrocytes and neurons that has been shown to naturally inhibit oligodendrocyte differentiation and myelination.7 This protein was also found to have increased expression in oligodendrocyte precursors from MS lesions.8 These discoveries led to the hypothesis that LINGO-1 inhibitors may enhance remyelination, which was later demonstrated using an anti-LINGO-1 antibody in several animal models of demyelination.9 LINGO-1 is a leucine-rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein shown to interact with EGF, ErB2, NgR1, and TrkB receptors in the CNS.8 BIIB033 is thought to disrupt some or all of these interactions, leading to the activation of pathways critical for myelination (figure).

Most monoclonal antibodies, and BIIB033 is no exception, have low penetration into the CNS, which suggests that very high doses may be required to obtain a therapeutic effect. In this article, as well as in the ongoing phase II trial, doses up to 100 mg/kg were used. The researchers measured the concentration of BIIB033 in CSF and concluded that doses higher than 10 mg/kg may result in concentrations in the CNS equivalent to those shown to enhance remyelination in animal models of MS. Surprisingly, in this study, the concentration of BIIB033 in the CSF did not appear to correlate with the dose administered, which will need to be further clarified in future studies.

One of the drawbacks of antibody therapies is that patients may develop an immune response against the therapeutic molecule, rendering the drug no longer useful in those patients. In this article, they evaluated the rate of production of antibodies against BIIB033 and found it to be low. While this is encouraging, in this study the patients received only 1 or 2 doses of the drug, which is not representative of the therapeutic paradigm in the long-term. Unfortunately, they also found antibodies against BIIB033 in one placebo-treated individual (false-positive), which indicates that a better assay may be needed.

Perhaps the biggest challenge for bringing myelin repair therapies to the clinic is how to monitor efficacy. Although the goal of this phase I trial was simply to assess safety and tolerability, they did include several diagnostic endpoints to assess myelin integrity. The patients were subjected to conventional and

See article
nonconventional MRI. Not surprisingly, the authors found that conventional MRI, as well as fluid-attenuated inversion recovery and diffusion tensor imaging, were not very useful to detect changes in myelin. They also used magnetization transfer ratio, a novel MRI technique that aims to show myelin changes,10 which appeared promising. Nevertheless, accurate methods to assess remyelination are critical, and to date there are no fully validated tools to quantify this reparative process. Other ongoing research efforts to develop approaches to monitor changes in myelin include tracers for PET, which may provide the sensitivity and specificity required for this important task.

The phase II trial for BIIB033 will be carried out in combination with Avonex (interferon beta), which is one of the front-line anti-inflammatory MS drugs currently in use. This is an important consideration, since the newly formed myelin will need to be protected from the autoimmunity that resulted in the demyelination in the first place. It will be encouraging if this combinatorial approach provides benefit equivalent to the more potent, and risky, anti-inflammatories currently used when the front-line therapies fail to provide benefit.

We have now reached a potential turning point in MS therapeutics. Over the past decade considerable effort has been exerted to develop therapeutic strategies to enhance myelin repair. These attempts have been based largely on a significant body of data that has defined the intrinsic and extrinsic factors that drive oligodendrocyte maturation and the myelination process. The anti-LINGO-1 trial is likely the first of many that will test drugs that have been shown to enhance remyelination in murine models. Soon we should know whether this approach will provide benefit to patients with MS, which would be the first evidence that enhancing myelin repair may alter the course of this disease. Although the jury is still out on the phase II trial, the phase I verdict is promising.

STUDY FUNDING
No targeted funding reported.

REFERENCES
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