

## **Long term clinical improvement with remyelination is less likely in MS**

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The precise cause of multiple sclerosis (MS) is still unknown and the disease pathology is complex. Despite the long held assumption of a primary myelin-specific autoimmune process in MS, no myelin-specific autoimmune reaction has so far been identified. Demyelination is one of the key pathological changes in MS, but not the only one. Disability progression in MS is the cumulative effect of chronic and diffuse neurodegenerative process in the grey and white matter of the brain and spinal cord. This is clearly shown in primary progressive multiple sclerosis (PPMS) where the burden of cerebral demyelinating lesion is relatively low. Multi-focal demyelination in brain is considered to be the hallmark of relapsing remitting MS but functional improvement after a clinical demyelinating episode occurs spontaneously over time, even in patients with large (tumefactive) cerebral demyelination.

Spontaneous remyelination in MS lesions is either restricted to the lesion edge or extends through the entire lesion area (shadow plaques); these remyelinated plaques may become the future target of new demyelinating events. Shadow plaques are commonly observed in the brain and spinal cord of MS patients and in one post-mortem study, white matter lesions were remyelinated in nearly half of all cases (47%) on average and 22% of them were found to be fully remyelinated. Even during plaque development, remyelination may occur very rapidly and ongoing myelin breakdown may coexist with areas of remyelination. There is no evidence that the number of shadow plaques or early remyelination correlated with better functional preservation in patients with any form of MS.

Several attempts have been made over the years to promote remyelination in MS. The concept that remyelination would prevent axonal loss and neuronal degeneration in MS leading to long term improvement however is not established in clinical studies. In animal models of EAE, natural occurring autoantibodies or intravenous immunoglobulins (IVIg) have been shown to successfully induce remyelination; however, human IVIg is not effective as a treatment in MS. Several remyelination pathways have recently become targets of new drug development in MS, including those of LINGO-1, hyaluronan, Notch-1, retinoid X receptor; targets also include pathways involving chemokine receptor type 4 and G protein-coupled receptor 17. There are also a number of existing ("re-purposing") drugs claimed to enhance remyelination, such as benztropine, clemastine, quetiapine, olesoxime, and ibudilast. However, there is not enough evidence that any of these drugs could be effective in promoting remyelination beyond the level that naturally occurs in MS.

Therapeutic attempt at remyelination in MS is at best likely to be partial or incomplete; remyelination alone would not prevent recurrent myelin injury or restore axonal integrity that has already been lost or irreparably damaged. If one takes the view that MS being primarily a neurodegenerative disease with secondary inflammation leading to focal perivenous demyelination in metabolically vulnerable areas of brain and spinal cord, then it is even more difficult to speculate meaningful and long term clinical improvement from therapeutic remyelination in MS. Cortical atrophy occurs before substantial white matter demyelination in MS and predicts future disease progression. A characteristic feature of MS is the disease pathology involving normal-appearing cerebral white and grey matter which inexorably increases in severity with disease and disability progression. It seems unlikely that remyelination will reverse these changes and reduce long term disability progression. The likely physiological benefit of remyelination would be improved nerve conduction and reduced ephaptic transmission rather than protection of cerebral grey or white matter from progressive MS pathology.

The recently reported clinical trial outcome of anti-LINGO antibody in acute optic neuritis showed electrophysiological improvement in about 40% patients without clinical benefit; it is

not known if some of the treated patients enrolled in this trial might have progressed to relapsing remitting MS. LINGO-1, its signalling partner proteins and pathways have been implicated in several neuropsychiatric disorders and antagonists of LINGO-1 may clinically benefit MS patients possibly for reasons other than remyelination.

The appropriate imaging marker of remyelinating lesions in MS is not yet established and its correlation with conventional MRI parameters of disease progression (brain volume loss and spinal cord atrophy) is still completely unknown. Until there are robust clinical trial data supported by imaging markers to confirm sustained functional recovery and prevention of disease progression in MS, the expectation of long term clinical improvement from remyelination therapy would be purely speculative.