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Editorial

Pushing Forward To Stop Progression and Reverse Disability in Multiple Sclerosis

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Abstract

Over the last decades, pharmaceutical companies have developed multiple treatments to help prevent relapses in early MS and clinicians can now tailor treatments to individuals based on risk factors and disease aggressivity. We are now at an inflection point in the history of MS management, where pharmaceutical focus will shift to treatment of other aspects of multiple sclerosis pathology. Several avenues in MS treatments will be investigated more thoroughly, such as progression prevention, neuroprotection and repair of MS pathology. MS progression may be tamed by extinguishing innate immune mechanisms possibly responsible for clinical progression. Trials for progression mitigation are complicated by financial costs, large time commitments as well as unresolved methodological questions. Neuroprotective agents may also limit progression, but no confirmed neuroprotective agents have been identified as yet in humans, and clinical trials run the risk of increased relapses and clinical worsening. Repair through remyelination treatments is an active area of pharmaceutical interest with numerous small trials currently running. Stem cells treatments offer a new blueprint for a potential MS management, though many to date have illustrated no utility in arresting progression and considerable safety issues exist with this approach. Many different avenues of research remain to be explored for effective MS treatment and in particular to halt progression and disability.

Keywords: Multiple Sclerosis; Neuroprotection; Progression; Remyelination; Repair

We are in a unique time in the history multiple sclerosis treatment. Never before have we had as many treatments for MS. Never before have we had so many strongly effective medicines as well, including natalizumab, alemtuzimab, and even rituximab. Barring unforeseen developments, we will likely soon have two additional rituximab-like drugs: ocrelizumab and ofatumamab. With the emergence of these treatments, we have in all practicality completed the development of treatments for the relapsing component of MS.

This may be puzzling for some to say this. Natalizumab is "only" effective in relapse reduction by ~70% [1]. This appears also to be the case for alemtuzimab, rituximab, and rituximab-like treatments [2-4]. However, side effects and risks suggest that anything more effective than these treatments would likely entail even higher side effects and risks. Progressive multifocal leukoencephalopathy (PML) risk is a considerable concern for those on natalizumab [5,6] and to a smaller degree rituximab [7]. Thyroiditis and immune mediated thrombocytopenia are also concerns for alemtuzimab [8,9]. Long-term use of alemtuzimab or what to do after stoppage of alemtuzimab is also not clear. Thus, with more effective MS treatments come associated risks, side effects and questions that are more unpalatable. Furthermore, with the high number of treatments now available, it is also unlikely that pharmaceutical companies will expend huge resources to develop a treatment that could get shot down more easily in this environment.

Thus, it is time to move on to treating other big issues of MS. In our view, these are progression prevention, neuroprotection, and repair. Clearly, progressive disease is a huge concern for patients and clinicians alike. Historically, RRMS patients go on to develop progressive phenotype 50-85% [10]. Interestingly, most patients are concerned about primarily this. Winding up in a wheel chair scares MS patients much more than transient relapses, even if severe. The problem there is manifold. First, it is still unknown what causes progression. One current theory is innate immune mechanisms within the brain are still active even in with ongoing treatment, such as with the interferon's, glatiramer, and possibly even natalizumab [11]. These innate immune mechanisms, meaning activated microglia and reactive astrocytosis within the CNS, may smolder and slowly promote demyelination, axonal injury and neurodegeneration. It is thus very exciting that some treatments that penetrate the brain, including fingolimod, dimethyl fumarate, and laquinimod, are available or are close to available for MS patients [12-17].

However, clinical trials examining effects of treatments on progression have been essentially negative [18]. Study design is an additional problem for development of treatments for progressive MS, since progressive MS occurs on a slower timescale than relapsing MS. Unfortunately, it appears that fingolimod showed no benefit in a PPMS trial recently (personal comm., Novartis). However, a dimethyl fumarate trial is about to begin and a natalizumab trial is completed for SPMS (NCT01416181). In addition, a laquinimod progressive trial may start soon.

Another great idea in MS management is to develop neuroprotective treatments. We need to protect neurons and axons

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from damage and degeneration, which should prevent disability. Good neuroprotection may help slow progression as well. Research suggests that inflammation causes mitochondrial energy failure and neuronal depolarization [19]. Persistent sodium influx through Nav1.6 channels causes reversal of Na+/Ca2+ exchanger, with sodium efflux and calcium influx. Calcium influx promotes further axonal injury with activation of nitric oxide synthase, proteases, and lipases.

Only a very few neuroprotective clinical trials have been attempted most likely due to financial support issues. The main thrust of interest has been with sodium channel blocking medicines. Unfortunately, a 2 year trial using 400 mg/day lamotrigine in secondary progressive MS (NCT00257855) showed lamotrigine had no significant effect on brain atrophy [20]. Lamotrigine did reduce deterioration of timed 25-foot walk, although a few patients exhibited worsening gait with lamotrigine use [20]. Other proposed trials including one using phenytoin in primary progressive MS and another using topiramate in relapsing remitting MS have not been completed or were halted. The chief concern in these studies was a theoretical risk of relapse after medicine withdrawal. Clinical worsening from a surge in inflammatory infiltrate in cords of EAE mice has been observed once sodium channel blocking medicine like phenytoin or carbamazepine was withdrawn [21]. Rebound clinical worsening may be avoidable by tapering sodium channel blocking medicines [22]. As a result, several trials are ramping up studying oxcarbazepine and phenytoin in MS or optic neuritis in England.

Other targets for neuroprotection are numerous and proliferating. These include targeting the neurotoxic cascade delineated above, including Na+/Ca2+ exchanger, nitric oxide synthase, proteases, and lipases [19]. In addition, other possible medical interventions to neuronal injury in general include glutamate antagonists, NAALADase inhibitors, HDAC (histone deacetylase) inhibitors, cannabinoid agonists, free radical scavengers, mitochondrial support [23]. A new trial, MS-SMART, is designed to assess effect of riluzole, a sodium channel blocker/NMDA receptor blocker, as well as amiloride, a sodium channel inhibitor, and ibudilast, a PDE4 inhibitor (NCT01910259). Additional agents may be identified with detailed review of other neuroprotective trials in other neurological diseases, including ALS, stroke, Alzheimer's disease, and others.

Repair is another important need in MS treatment. Since damage can occur to myelin and to neurons/axons, both should be targeted in treatment development. To date, most clinical work has focused on remyelination treatments, including anti-LINGO antibodies, anticholinergic medicines, antihistamine treatments, and rhIgM22 [24,25]. Clinical trials are ongoing with anti-lingo antibodies in MS (NCT01864148) and in optic neuritis (NCT01721161). Preliminary phase II clinical trial data released recently indicate that anti-lingo treatment partially normalized optic nerve latency by evoked potentials (NCT01721161). For rhIgM22, phase I data show that rhIgM22 is safe at all doses studied (NCT01803867). A small clinical trial examining clemastine, an antihistamine, anticholinergic medicine, for remyelination in MS is ongoing (NCT02040298). A phase 2 trial examining GSK239512, an antihistamine medicine, for remyelination in MS recently completed (NCT01772199). Other good targets for enhancing remyelination in MS, including hyaluronidase, Toll-like receptor 2, wnt/B-catenin, RXR receptor, Notch-1, CXCL12/CXCR4, and GPR17, are at a preclinical stage only [24,25].

Neuroregeneration is an important secondary goal in MS. Anti-inflammatory MS treatments may allow for axonal regrowth and synaptic plasticity to improve. Anti-LINGO treatment may also enhance axonal regrowth [26]. However, these treatments are probably not enough for substantial neuroregeneration, especially in cases of progressive MS exhibiting T1 hypointensities and atrophy to brain and cord.

Stem cell treatments have potentially two functions in MS treatment: stopping immune-mediated damage and enhancing repair and regeneration. Hematopoietic stem cell transplantation has tremendous potential to reset the immune system and arrest inflammatory relapses. Multiple studies dating back to 1998 have shown a modest to substantial benefit in MS [27]. Two recent studies showed nonmyeloablative hematopoietic stem cell transplantation in conjunction with strong immunosuppression stabilized inflammatory activity and improved neurological disability [28,29]. Interestingly, many of these studies also show no benefit to arresting progression while stopping relapsing inflammatory activity [27].

While intrinsic mechanisms within the brain may enhance remyelination and neuroregeneration in MS, these processes are demonstrably limited. Thus, medical treatments, including mesenchymal stem cell transplants may assist these processes and prevent progression [27]. However, there are significant issues and risks with this procedure, such as infusion-related toxicity, infections, and ectopic tissue formation [30]. There is also little standardization of dosing and optimal culture regimen. Much work remains to be done in this arena.

Overall, targets have been identified to address progression, neurodegeneration, and loss of myelin in MS. Clinical trials for each of these problems in MS are developing. This process is required to advance beyond the focus of immunomodulatory/immunosuppressive treatments now that there are many such treatments. Many new trials are near completion or starting to determine whether MS treatments curtail progression. Neuroprotection is an important goal but does not have as much interest at present. Remyelination is beginning to garner interest, especially with anti-Lingo and rIgM22 trials underway. Stem cell treatments have the dual potential of curtailing autoimmune dysfunction as well as permitting repair and neuroregeneration. Thus, there are many reasons to be excited about the future of MS treatments for progression, neuroprotection, and repair.

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