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# 2014 Multiple Sclerosis Therapeutic Update

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**Abstract**

Rapid advances are occurring in multiple sclerosis disease modifying therapies. Recent therapeutic advances include modifications to improve tolerability of existing products (e.g. interferon beta and glatiramer acetate), development of novel anti-neuroinflammatory medications (e.g. fingolimod, teriflunomide and dimethyl fumarate, daclizumab, alemtuzumab, ocrelizumab) and investigation of treatments in progressive MS (e.g. natalizumab, mastinib, natalizumab, siponimod). The impact of vitamin D supplementation on the disease course in relapsing MS patients is also being studied in several clinical trials. This article reviews the current state of the field with a forward look to the next phase of MS research that could focus on strategies to promote remyelination and provide neuronal protection.

**Keywords**

relapsing multiple sclerosis, progressive multiple sclerosis, randomized controlled trials, clinical trials, therapeutics

Multiple sclerosis (MS) therapeutics is one of the most rapidly advancing areas in neurological research. Over the last 20 years, various forms of autoinjected interferon beta (IFN β) and glatiramer acetate (GA) became widely used as first-line disease treatments. Natalizumab, and to a much lesser extent mitoxantrone, are second-line intravenously infused treatments. However, in the last few years 3 oral disease-modifying therapies were approved for relapsing MS: fingolimod, teriflunomide, and dimethyl fumarate. These therapies offer the advantage of oral bioavailability and will likely improve treatment adherence.

Two recent studies were designed to improve dosing regimens of currently approved treatments. The Glatiramer Acetate Low-frequency Administration (GALA, NCT01067521) study showed that thrice weekly subcutaneous (SC) GA 40 mg reduced the relapse rate at 1 year.[1] The Efficacy and Safety Study of BIIB017 (ADVANCE, NCT00906399) study showed that SC pegylated IFN β-1a reduced the relapse rate and slowed 1-year disability progression in patients with relapsing MS.[2] Thrice weekly GA has already received US Food and Drug Administration's (FDA) approval and it seems likely that pegylated IFN will as well. Results of 2 phase III trials of oral teriflunomide, a pyrimidine de novo synthesis inhibitor that blocks the enzyme dihydroorotate dehydrogenase, were also presented. The Teriflunomide in Patients With Relapsing Multiple Sclerosis (TOWER, NCT00751881) study showed teriflunomide's efficacy in reducing the relapse rate and neurological impairments in MS over 2 years.[3] The Teriflunomide versus placebo in patients with first clinical symptom of multiple sclerosis (TOPIC, NCT00622700) study showed teriflunomide's impact on delaying the time to the second clinical attack in patients who presented with an initial demyelinating event who had lesions on brain magnetic resonance imaging (MRI) suggestive of MS.[4]

Alemtuzumab, a monoclonal antibody that depletes lymphocytes and monocytes, successfully completed 2 large phase III trials, resulting in approval of use in over 30 countries (comparison of alemtuzumab and Rebif efficacy in multiple sclerosis: CARE MS 1-NCT00530348 and CARE MS 2- NCT00548405). However, the US FDA did not approve alemtuzumab because of concerns that the studies' designs did not provide sufficient evidence of efficacy, given alemtuzumab's complex safety profile. Alemtuzumab treatment is associated with de novo autoimmune thyroid disease, immune thrombocytopenic purpura, and Goodpasture nephropathy. There is still an unmet need for efficacious therapies in patients who have highly active MS who cannot receive treatment with natalizumab. It is precisely this niche that alemtuzumab might have filled.

Several phase III studies in relapsing MS are ongoing. Second-generation sphingosine-1-phosphate receptor 1 modulators show promise in reducing some of the side effects associated with fingolimod including bradycardia, liver function abnormalities, and pulmonary fibrosis (siponimod, RPC-1063,

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ONO-4641, ponesimod). Several monoclonal antibodies are also in development for relapsing MS and include daclizumab and ocrelizumab. Furthermore, a higher dose of laquinimod, an orally bioavailable molecule that showed possible neural protective properties in phase III, is being studied.

One of the most pressing unmet needs for MS is the development of disease-modifying treatments that slow disability accumulation in progressive forms of MS. Currently, none of the marketed antineuroinflammatory therapies are approved for either primary progressive MS (PPMS) or secondary progressive MS (SPMS; perhaps with the exception of IFN β-1b in Europe). Therefore, several clinical trials in progressive forms of MS are of great clinical interest. If successful, the FTY720 in Patients With Primary Progressive Multiple Sclerosis (INFORMS) would be the first clinical trial of any therapy to show an impact of treatment on disability progression in this disease subtype (NCT00731692). This study could also lead some credence to the hypothesis that sphingosine-1-phosphate receptor modulation might have neuronal protective properties. A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Subjects With Secondary Progressive Multiple Sclerosis (ASCEND) also warrants attention (NCT01416181). Although very late antigen 4 receptor blockade in relapsing forms of MS has a strong theoretical basis, it is far less certain whether this mechanism of action will also apply to SPMS. A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis (ORATORIO; NCT01194570) follows a post hoc subgroup analysis of an earlier study of rituximab, a monoclonal antibody that depletes B-cells, in PPMS in which younger patients (<55 years) and those who had contrast-enhancing lesions on baseline brain MRIs seemed to benefit from treatment. A study of a mast cell inhibitor (masitinib) in patients with progressive disease who do not have relapses is also ongoing (NCT01433497).

Therapies that could protect the nervous system from the consequences of inflammatory injury, so-called neural protection, and therapies that might promote remyelination or neuronal regeneration are of great interest. Several early trials are being conducted to address these potential therapeutic modalities. A phase II study of neural protection will explore whether the compound NT-KO-003, a putative inhibitor of microglial activation, may have neuronal protectant properties (NCT01428726). Widespread microglial activation is a histopathological hallmark of progressive MS and inhibition of this aspect of innate immunity could potentially have beneficial effects on both progressive and relapsing forms of MS. A phase II trial of phenytoin will determine whether this drug preserves the thickness of the retinal nerve fiber layer following optic neuritis (NCT01451593). Phenytoin could theoretically prevent sodium entry into demyelinated axons, thereby protecting them from injury. A phase II study (NCT01489254) will assess whether GSK239512, a small molecule histamine H-3 receptor antagonist, can promote remyelination as measured by the recovery of the magnetization transfer ratio in actively inflamed brain lesions. Magnetization transfer ratio is a quantitative MRI measure that might be a radiographic surrogate marker for shadow plaque formation. A phase II study of clemastine, an antihistamine that may promote oligodendrocyte remyelination, is ongoing in patients with MS with a history of optic neuritis and will use several methods to detect evidence of optic nerve remyelination (NCT02040298). Two phase II studies of anti-LINGO, a monoclonal antibody that promotes remyelination, are ongoing: one in optic neuritis (NCT01721161) and one in relapsing MS (NCT01864148). It seems likely that these studies are sentinels of a new wave of studies intended to identify medications that may protect or even heal the nervous system. These medications will likely be used as adjuvants to existing antineural inflammatory therapies.

The recent identification of vitamin D as a risk factor for MS susceptibility, and more recently as a potential modifier of disease course, inspired several clinical trials in relapsing MS (NCT01728922, NCT01753375, NCT01768039, NCT01490502). These studies will determine whether vitamin D supplementation acts as a disease-modifying therapy. In practice, many patients already supplement with vitamin D. However, it is not known whether supplementation has a direct impact on the MS disease course. If successful, these studies will help answer the question as to how much vitamin D the patients with MS should supplement as well as what level of 25-OH vitamin D one should target for optimal benefit.

Over the last 20 years, industry sponsored research brought to market 10 disease-modifying therapies for relapsing MS. Somewhat paradoxically because of this success, further development of novel anti-inflammatory therapies in relapsing MS could draw to a close in the next few years. Industry support for new trials with antineuroinflammatory therapies may wane when lower cost generic therapies become available. It seems unlikely that government-funded, or society-sponsored, research will be able to provide the necessary resources for continued development of such therapies. As a consequence, it is conceivable that it is already too late for potentially useful anti-inflammatory treatments in early development to reach the MS market in time for commercial success.

## Declaration of Conflicting Interests

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