New oral disease-modifying therapies for multiple sclerosis
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Abstract
Several promising, oral disease-modifying therapies for multiple sclerosis are currently being evaluated in clinical trials. The arrival of effective oral agents for multiple sclerosis will be a major advance in the global effort to alter the natural history of this chronic disease.

Introduction and context
In the past 15 years, six new drugs have been approved by the US Food and Drug Administration (FDA) as disease-modifying therapies (DMTs) for multiple sclerosis (MS). All of these agents are either infusions or self-administered injections, and many patients report symptoms of pain, anxiety or injection-site reactions associated with these treatments. Such side effects negatively impact some MS patients’ satisfaction and compliance with available DMTs, and there are even MS patients who forgo DMTs altogether because of difficulties associated with injections. Currently, there are several promising oral DMTs for MS in phase II and III clinical trials (Table 1). The arrival of oral DMTs for MS will represent a major advance in MS therapeutics.

Recent advances
Cladribine is a purine nucleoside analogue that preferentially depletes lymphocytes [1]. It is currently FDA-approved in its injectible form for the treatment of hairy cell leukemia. Cladribine has shown promise as a DMT for MS in its injectible form in several clinical trials, especially with regard to suppression of gadolinium-enhancing lesions [2–4]. In an 18-month trial of injectible cladribine in relapsing-remitting MS patients, treated patients had significant reductions in relapse rate and gadolinium-enhancing lesions on magnetic resonance imaging (MRI) compared to placebo [4]. An oral formulation of cladribine for MS is currently in phase II and phase III clinical trials, both as monotherapy and in combination with interferon beta-1a (INF beta-1a), and has been designated by the FDA as a fast-track product for expedited review. Cladribine has shown to be generally well-tolerated in previous trials, but the risk of infection and bone marrow suppression associated with its long-term use is yet to be determined [5].

Laquinimod, a derivative of linomide, is thought to limit the infiltration of leukocytes into the central nervous system and to shift the lymphocyte populations towards Th2/Th3 cytokine expression [6]. A phase II trial of oral laquinimod showed that the drug was well-tolerated by MS patients, and that it significantly reduced gadolinium-enhancing lesions compared to placebo after 24 weeks [7]. Unlike linomide, which ultimately failed in clinical trials as an MS drug because of serious adverse cardiovascular events, laquinimod has not been associated with any such side effects [7,8]. Oral laquinimod is currently being evaluated in a series of phase III clinical trials.

Fingolimod (FTY-720) is a sphingosine-1-phosphate receptor modulator that prevents egress of lymphocytes outside of lymph nodes, the effect of which significantly reduces the number of circulating lymphocytes [9,10]. Specifically, it reduces the number of naïve and memory T cells but not effector T cells, and it does not affect T-cell function [9]. In a phase II trial of 255 MS patients, oral fingolimod significantly reduced the number of gadolinium-enhancing lesions and the annualized relapse rate...
compared to placebo [10]. Oral fingolimod is currently being evaluated in phase III trials. The safety and tolerability of fingolimod remains questionable, as two serious adverse infections were reported in the extension phase of the phase II study [10].

Teriflunomide is a metabolite of leflunomide, an FDA-approved treatment for rheumatoid arthritis [11]. A chemotherapeutic agent, oral teriflunomide blocks pyrimidine synthesis by inhibition of dihydro-orotate dehydrogenase, and ultimately interferes with the interaction of T cells with antigen-presenting cells, thereby inhibiting T-cell activation [6,12–14]. Teriflunomide has also been shown to suppress experimental allergic encephalomyelitis (EAE), a murine model of MS [14]. In a 36-week, phase II trial, oral teriflunomide significantly reduced the number of combined unique active lesions on MRI in MS patients compared to placebo and was well-tolerated by patients [15]. It is currently undergoing phase III trials as monotherapy, and in combination therapy with both IFN beta-1a and glatiramer acetate.

BG00012 (fumarate) is an immunomodulatory agent that is used to treat psoriasis. Oral BG00012 has been shown to suppress the number of CD4+ and CD8+ lymphocytes in peripheral blood, and to cause a shift in T-cell cytokine production away from a Th1 profile and towards a Th2 profile [16,17]. A phase II, 24-week clinical trial of BG00012 showed a significant decrease in gadolinium-enhancing lesions, new T2 lesions, and hypointense T1 lesions on MRI in MS patients compared to placebo, and was found to be generally well-tolerated [18]. A phase III trial of oral BG00012 in MS is currently underway.

Minocycline is an FDA-approved oral antibiotic that is recognized to have both anti-inflammatory and neuroprotective properties, and is safe and well-tolerated. Minocycline has been shown to inhibit matrix metalloproteinase-9 activity, which is important to lymphocyte migration into the central nervous system, and inhibits microglial activity and apoptosis in vitro [19]. Minocycline has also been shown to inhibit EAE [20]. In a small, open-label trial of minocycline in MS, the proportion of active MRI scans during the treatment was significantly lower than in the run-in phase [21]. Minocycline is currently in a phase III trial as monotherapy for MS, and in phase II trials as adjunctive therapy with glatiramer acetate and INF beta-1a.

Mycophenylate mofetil is an oral immunosuppressive agent that is FDA-approved to prevent organ transplant rejection. It inhibits the synthesis of purines used in the proliferation of T and B lymphocytes [22]. A phase II trial in MS of mycophenylate mofetil as adjunctive therapy to INF beta-1a showed a significant reduction in relapse rate after 6 months on combination therapy compared to INF beta-1a monotherapy [23]. Oral mycophenylate mofetil is currently in phase III trials as an adjunctive DMT with INF beta-1a.

HMG-CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase inhibitors, the so-called ‘statins’, represent a group of oral medications that are approved to treat hyperlipidemia and that are generally well-tolerated. Statins are also recognized to have immunoregulatory activity. Specifically, statins have been shown to suppress EAE through a shift from Th1 to Th2 cytokine production and inhibition of lymphocyte migration across the blood brain barrier [24]. A phase II, open-label clinical trial of high-dose atorvastatin in MS showed a significant reduction in the number and volume of gadolinium-enhancing lesions after 9 months [25]. However, one small study of high dose atorvastatin versus placebo as adjunctive therapy with INF beta-1a showed that MS subjects in the atorvastatin group were significantly more likely to have clinical or MRI disease activity after 6 months compared to those on placebo [26]. Pravastatin is currently in a phase III trial as monotherapy for MS.
and simvastatin is in a phase III trial as adjunctive therapy with INF beta-1a.

Vitamin D deficiency has recently been associated with a higher risk of developing MS in a sero-epidemiological study, and vitamin D intake appears to be associated with a decreased risk of developing MS [27,28]. Vitamin D3 production is stimulated by sunlight exposure, and the recent vitamin D observations in MS may explain the long-observed phenomenon of higher MS prevalence in geographic areas where sunlight exposure is relatively low. Vitamin D is also known to have immunomodulatory properties, especially with regard to T-cell regulation [29]. A phase II trial of high-dose, oral vitamin D3 therapy in MS as a DMT is currently ongoing.

Implications for clinical practice
Several promising oral agents are currently being evaluated in clinical trials as DMTs for MS, and the likelihood is that at least some of them will gain FDA approval. The arrival of these oral agents will give MS patients and MS physicians more therapeutic options, which will be especially beneficial for those MS patients who have difficulty with injections or who have experienced intolerable side effects from the currently available DMTs. Another important benefit of the emergence of oral DMTs is that there is likely to be a reduction in the overall expense of MS therapeutic care. While some of these therapies are currently approved for other indications, we do not recommend off-label use of these oral drugs until results from phase III trials are available. These agents may prove to be ineffective or even harmful and may encourage patients to avoid FDA-approved therapies. The availability of oral DMTs with proven efficacy will represent a significant advance in the MS physician’s ability to treat all MS patients. The advent of oral DMTs will herald a new era of increased adherence to, and satisfaction with, therapy for MS patients.

Abbreviations
DMT, disease modifying therapy; EAE, experimental allergic encephalomyelitis; FDA, Food and Drug Administration; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; INF beta-1a, interferon beta-1a; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Competing interests
BAB declares that she has no competing interests. DB has research grants from the National Institutes of Health, the Department of Veterans Affairs, the National MS Society, BiogenIdec and Forest Laboratories and he has received honoraria for speaking and unrestricted educational grants from Teva Neurosciences, EMD Serono, and BiogenIdec.

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