Review Article

Update on Disease-Modifying Treatments for Multiple Sclerosis

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ABSTRACT

Purpose: The purpose of this review is to discuss the selection and use of disease- modifying treatments for patients with relapsing forms of multiple sclerosis (MS).

Methods: PubMed was searched (1966–2014) using the terms *multiple sclerosis, treatment, interferon, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide, natalizumab, rituximab*, and *alemtuzumab*.

Findings: MS is a chronic neurological disorder that can cause a substantial degree of disability. Because of its usual onset in young adults, patients may require treatment for several decades. Currently available agents include platform injectable therapies, newer oral agents, and second-line monoclonal antibody treatments. Treatment decisions have become more complex with the introduction of new approaches, and a major goal is to balance perceived efficacy and tolerability in a specific patient with the relative impact of disease activity and adverse events on quality of life. Here the options for disease-modifying treatments for relapsing forms of MS are reviewed, and current and future challenges are discussed.

Implications: An evidence-based approach can be used for the selection of disease-modifying treatments based on disease phenotype and severity, adverse events, and perceived efficacy. (*Clin Ther*. 2014;36:1938–1945) Published by Elsevier HS Journals, Inc.

Key Words: immune therapy, multiple sclerosis, interferon, glatiramer, natalizumab, fumarate.

INTRODUCTION

Multiple sclerosis (MS) is the most common cause of nontraumatic neurological disability in young adults and has a high personal and societal impact on quality of life and health-care costs.[1] Many options currently exist to treat relapsing forms of MS. These include platform injectable therapies, newer oral options, and targeted monoclonal antibody agents for those who require more aggressive therapy. All of these approaches have demonstrated efficacy at reducing the number of clinical relapses and appearance of new lesions on imaging. Although effects on long-term outcome are less clear, there is evidence that early treatment can reduce long-term mortality associated with MS disability.[2,3]

All current disease-modifying treatments modulate or suppress immune function, particularly within lymphocyte subsets.[4] The success of these approaches combined with numerous studies on immunology,[5,6] pathogenesis,[7,8] and genetics[9] has confirmed that MS is an immune-mediated disorder of the central nervous system (CNS). Because of the relatively high incidence of MS in some populations and the ability to monitor disease activity clinically and radiologically, the development of MS therapeutics has been at the leading edge of translational research in autoimmune and neuro-

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logical disorders. Here I review the currently approved agents, discuss the risks and benefits relevant to the aggressiveness of the disease course and perceived efficacy, and outline the longer term goals and challenges.

METHODS

Published studies relevant to treatment of MS were identified by a search of PubMed. The literature search was limited to the English language and had no limit on the year of publication.

First-Line Disease-Modifying Treatments

Platform Injectable Therapies

The platform injectable therapies include several β interferons* and glatiramer acetate.† The advantage of these agents is that they have >20 years of safety data, and serious adverse events occur rarely. The major disadvantages are that only a subset of patients responds to these treatments and the effect can be modest. Nevertheless, these agents have clearly benefited many patients. Their mechanism of action is targeted primarily at modulation of T lymphocyte differentiation[10] and function,[11] and, in general, they do not have a marked immunosuppressant effect.

Interferon-β (IFN-β) 1b was the first agent to demonstrate a clear effect on relapse rate reduction. This finding revolutionized treatment of MS patients and encouraged further development of disease-modifying treatments. In a pivotal trial, IFN-β 1b at a dose of 8 MIU every other day reduced the exacerbation rate by approximately one third in treated patients compared with the placebo group.[12]

Subsequently, other IFN-β formulations and dosage schedules have been shown to have similar efficacy,[13] and there may be a slight benefit of higher dose preparations during the first year of treatment.[14] Their long-term safety profile is relatively favorable. However, because of the possibility of transaminitis and hematological adverse events, laboratory monitoring of liver functions and blood count needs to be performed on a regular basis. In addition, many patients experience flu-like side effects of variable severity, and some patients may develop a worsening of depression. Ease of use of IFN-β may be increased in the near future by the introduction of a pegylated form, peginterferon-β 1a,‡ that will allow administration every other week.[15]

IFN-β is also approved for use in patients who have had a single clinical demyelination event and are at high risk of experiencing a second one. These patients are classified as having a clinically isolated syndrome. The risk of having a second clinical attack is primarily determined by magnetic resonance imaging (MRI) evidence of demyelinating-type lesions disseminated in space. For this patient group, treatment with once-weekly IFN-β 1a reduced the risk of a second relapse by approximately one third during a 3-year follow-up.[16] Subsequent studies demonstrated that treatment of a clinically isolated syndrome with other IFN-β preparations[17,18] and glatiramer acetate[19] also reduce the risk of a second event.

Unlike IFN-β, which is an endogenous cytokine and a biological agent, glatiramer acetate is a random copolymer synthesized from 4 amino acids that was designed to induce a tolerogenic immune response to myelin basic protein. However, it has a wide range of affinity for T-lymphocyte receptors and was found to suppress an encephalitogenic response to other related immunogens.[20] In the pivotal Phase III trial, glatiramer acetate at a daily dose of 20 mg reduced the relapse rate in treated MS patients by ~29% compared with the placebo group.[21] Trials that compared glatiramer to high-dose IFN-β suggest that the 2 treatments demonstrate similar efficacy on clinical outcomes but that IFN-β may have a more marked effect on imaging outcomes.[22,23]

For those patients starting on IFN-β or glatiramer acetate, approximately one third will remain on their initial choice and be relapse free within the first 2 years of treatment. Before the approval of newer oral agents, a large subset of patients switched to a second injectable platform treatment because of a lack of efficacy or because of adverse events, and some responded at least partially to the new treatment.[24] However, evidence of persistent disease activity while on treatment predicts increased accumulation of disability and suggests that patients with a more severe disease course should be considered for more aggressive treatments. Persistent disease activity includes clinical course and radiological findings; those

*Avonex® (Biogen Idec), Betaseron® (Bayer Healthcare), Extavia® (Novartis Pharmaceutical Corporation, Whippany, New Jersey), and Rebif® (Pfizer).

†Copaxone® (TEVA Neuroscience).

‡Plegridy® (Biogen Idec, Cambridge, Massachusetts).