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Therapeutic reviews

Currently approved and emerging oral therapies in multiple sclerosis: An update for the ophthalmologist

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ABSTRACT

Although our understanding of multiple sclerosis (MS) has grown substantially, its cause remains unknown. Nonetheless, in the past 3 decades, there have been tremendous advancements in the development of disease-modifying drugs (DMDs). In July 1993, the United States Food and Drug Administration approved the first disease-modifying drug—interferon β– and there are currently 13 medications approved for use in relapsing MS. All the early medications are administered either as a subcutaneous or intramuscular injection, and despite the clinical efficacy and safety of these medications, many patients were hampered by the inconvenience of injections and injection-related side effects. In September 2010, the first oral DMD—fingolimod—was approved. Since then, 2 additional oral DMDs (teriflunomide and dimethyl fumarate) have been approved, and several other oral medications are being evaluated in extensive MS development programs. Because of frequent ocular involvement, ophthalmologists are often involved in the care of MS patients and therefore need to be aware of the current treatment regimens prescribed by neurologists, some of which can have significant ophthalmic adverse events. We update the current advancements in the treatment of MS and discuss the published clinical data on the efficacy and safety of the currently approved and emerging oral therapies in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disease affecting the central nervous system (CNS). MS attacks myelinated axons within the CNS, resulting in demyelination and varying degrees of axonal damage, with consequent accumulation of disability over the course of disease. MS is thought to affect more than 2 million people worldwide and is a leading cause of disability in young people, affecting women twice as often as men, with age of onset typically between 20 and 45 years.[17] The disease course is highly variable and, in part because of its episodic nature, may be difficult to diagnose. There is currently no definitive diagnostic test available; therefore, the diagnosis is made largely on clinical grounds, often using a combination of magnetic resonance imaging (MRI), lumbar puncture, serologic testing,

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and evoked potentials.[90] Although the underlying cause of MS is not known, it appears to involve a combination of genetic and nongenetic factors, such as infectious, metabolic, and environmental triggers.[6]

Based primarily on clinical course, there are 4 generally recognized subcategories of MS[69]:

1. Relapsing-remitting MS (RRMS): the most common form, affecting approximately 85% of all MS patients. Characterized by episodic flare-ups (or relapses) of various neurologic symptoms, followed by periods of disease stability (i.e., remission).
2. Secondary progressive MS: develops over time after the diagnosis of RRMS with gradual worsening with or without superimposed relapses.
3. Primary progressive MS: affecting 8%–10% of patients, characterized by gradual continuous neurologic deterioration from onset.
4. Progressive-relapsing MS: the least common form, affecting less than 5% of patients. Progressive from onset (similar to primary progressive MS), but with superimposed relapses.

Since the original description of sclerotic brain lesions in the mid-19th century, and until only recently, treatment options for MS were limited primarily to corticosteroids and potent immunosuppressant agents (cyclophosphamide, methotrexate). In 1993, the United States Food and Drug Administration (FDA) approved the first disease-modifying drug (DMD) for the treatment of RRMS. Interferon beta-1b was a major milestone in MS therapy, serving as the first step in almost three decades of MS drug development. There are now 13 FDA-approved DMDs for the treatment of RRMS, with several more agents in various stages of development.

Because optic neuritis is the initial demyelinating symptom in 15%–20% of patients and can occur in up to 50% of patients at some point in their disease, ophthalmologists are frequently involved in the clinical care of patients with MS.[3,5,37] We update ophthalmologists on the available parenteral DMDs, with an emphasis on the newer oral DMDs, as well as some of the emerging therapies for MS. We will begin by reviewing the clinical and paraclinical metrics that are used as study outcome measures to set the foundation for understanding the outcome of the phase III clinical trials that are vital to the approval of DMDs into the MS treatment armamentarium.

2. Clinical trial outcome measures

There has been a marked evolution in clinical outcome measures since the development and execution of early MS treatment trials. Early studies were primarily designed to assess the treatment response compared to placebo, focusing on relapse reduction in patients with established RRMS. Later trials sought to determine whether early intervention could delay disability accumulation. With an expanding arsenal of therapies and robust evidence that early intervention can delay disability onset, it has become increasingly difficult (and in some cases unethical) to enroll patients in placebo-controlled treatment trials.[91] As treatments and technologies have evolved over time, so has the design of clinical trials. Outcome measures in newer trials not only assess clinical relapses, but also have expanded to include a variety of MRI metrics, disability assessment, low-contrast visual acuity, optical coherence tomography (OCT), and various other clinical and paraclinical outcomes.[64]

2.1. *Clinical relapse*

A clinical relapse (or exacerbation) is defined as an episode of neurologic dysfunction lasting at least 24 hours not attributed to another cause, such as stroke or infection.[55] A variety of outcomes have been developed to assess clinical relapses in a quantifiable, objective fashion. Annualized relapse rate (ARR), time to first relapse, and conversion to clinically definite MS (CDMS) have been the most common primary outcome measures used to date.[64]

ARR is frequently included as a primary outcome measure because it is easily quantifiable within the typical 1- to 2-year follow-up period of a trial. ARR is defined as the mean number of relapses in a cohort within 1 year[1]; however, owing to a variety of factors (i.e., few relapses), it is becoming more difficult to demonstrate a difference in treatment groups with this metric, requiring larger cohorts to reach statistical significance.[51,102] Compared to ARR, time to first relapse is possibly a more appealing outcome measure because it may allow for a shorter length of enrollment time, as well as a smaller sample size, and is also a relatively easy metric to monitor.[102]

Conversion to CDMS is an assessment of the time from an initial demyelinating event, or clinically isolated syndrome, to CDMS based on evidence of dissemination in time. CDMS was used as an endpoint in the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) and Early Treatment of MS Study (ETOMS), which led to the practice of treating clinically isolated syndrome patients with a high-risk MRI.[26,52]

2.2. *Disability progression*

A primary endpoint for clinical trials should generally be a clinical event that the patient is aware of and wishes to avoid in the future.[36] In MS trials, disability would be the most obvious choice; however, disability progression can be a difficult endpoint to define or to measure reliably.[64] Because MS has a wide range of clinical manifestations, the construction of a single, effective, reliable rating system for disability is lacking.

The expanded disability status scale (EDSS) was devised to assess patients' disability across a variety of functional systems, including visual, motor, sensory, coordination, cognitive, and mobility evaluation (Fig. 1).[63] The EDSS is frequently used in clinical trials but has several shortcomings. In particular, it has poor sensitivity to change, subjective low-score values, and a heavy bias toward mobility, with low interrater and intrarater reliability.[45]

The MS functional composite attempts to address some of the limitations of the EDSS. The MS functional composite, a brief test that is relatively easy to administer and can be assessed by nonclinicians, consists of a 25-foot timed walk, a