CURRENT AND EMERGING MULTIPLE SCLEROSIS THERAPEUTICS

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ABSTRACT

For a disease whose cause remains elusive, there has been a paradoxical growth in multiple sclerosis (MS) therapeutics. During the past 17 years, six therapeutic drugs for MS were brought to market. All of these disease-modifying therapies (DMTs) have shown a beneficial effect in reducing the number of exacerbations in double-blind placebo-controlled trials, and three drugs (subcutaneous [SC]/IM interferon beta-1a, natalizumab) have been shown to reduce relapses, decrease MRI activity, and reduce the risk of sustained disability after 2 years of treatment. No controlled studies exist to show long-term benefit with any of the current DMTs. Immunosuppressive drug (ISD) therapies continue to play a role in the management of patients who fail to respond to immunomodulatory agents. These agents, however, have shown mixed data in terms of efficacy and put patients at higher risk for the development of secondary cancers. Plasma exchange for severe relapses not responsive to corticosteroid therapy has regained interest in the past few years. Furthermore, six new agents that will dramatically impact our ability to prevent disability in patients with MS are in late-stage or have completed phase 3 clinical development. Determining the risk-benefit calculations that we will need to employ toward these new drugs and the algorithms for switching therapies will be critical issues in the next 5 years. This article highlights the clinical efficacy of the current DMTs/ISDs and discusses the current treatment options for clinically isolated syndrome, relapsing-remitting MS (RRMS), and exacerbations of RRMS. It also addresses the management of a suboptimal response to the DMTs; discusses the challenge of primary progressive MS; and presents an overview of emerging therapeutic options.

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Note: Text referenced in the Quintessentials Preferred Responses, which appear later in this issue, is indicated in yellow shading throughout this article.

DISEASE-MODIFYING THERAPIES

The decade of the 1990s brought forth the first US Food and Drug Administration (FDA)-approved disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS). Interferon beta-1b (Betaseron) was approved in 1993, glatiramer acetate (Copaxone) in 1996, IM interferon beta-1a (Avonex) in 1997, and subcutaneous (SC) interferon beta-1a (Rebif) in 2002 (**Table 3-1**).

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Greenberg discusses the investigational use of multiple agents, including alemtuzumab, BG00012, daclizumab, FTY720, laquinimod, and teriflunomide. Dr Khatri and Mr Kramer have nothing to disclose.

More similarities than differences exist among these agents, and all four reduce the number of relapses by approximately 30% (somewhat lower in the intent-to-treat analysis of the pivotal IM interferon beta-1a trial). Two drugs, SC and IM interferon beta-1a, showed a reduction in the risk of sustained disability at 2 years.[1,2] Researchers have retrospectively attempted to glean long term-data from population subsets in these pivotal trials to determine whether there is a long-term therapeutic benefit. With the known biases of retrospective analyses in mind, the long-term data show that certain subsets of patients in each of the pivotal trials do well on continuous therapy.

In general, the injectable DMTs are safe and well tolerated (**Table 3-1**). For patients on interferon therapy, hematologic abnormalities, including leukopenia, thrombocytopenia, and liver enzyme elevation, are well documented

KEY POINT

- More similarities than differences exist among the injectable disease-modifying therapies for multiple sclerosis (MS), and all four reduce the number of relapses by approximately 30%.

TABLE 3-1 Current US Food and Drug Administration–Approved Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Drug	Dosing	Mode of Action	Adverse Effects	Precautions	Pregnancy Category
Interferon beta-1a					C
(Avonex)	30 μg IM once a week	Promotes $T_H1 \rightarrow T_H2$ shift	Leukopenia LFT abnormalities	Obtain baseline and periodic LFTs and complete blood cell count	
(Rebif)	44 μg SC 3 times a week	Promotes $T_H1 \rightarrow T_H2$ shift	LFT abnormalities	Obtain baseline and periodic LFTs and complete blood cell count	
Interferon beta-1b					
(Betaseron/ Extavia)	8 mIU SC every other day	Has antiviral/ anti-inflammatory properties	LFT abnormalities	Obtain baseline and periodic LFTs and complete blood cell count	
Glatiramer acetate (Copaxone)	20 mg SC every day	Promotes suppressor cells of T_H2 Bystander suppression Possibly promotes brain-derived neurotrophic factor production	Injection site reactions		B
Mitoxantrone	12 mg/m^2 maximum dose 140 mg/m^2	Antineoplastic-anthracenedione class	Leukemia (0.44%–0.67%) Congestive heart failure	Preexisting heart failure or immunodeficiency	X
Natalizumab (Tysabri)	300 mg IV monthly	Prevents activated T cells from crossing the blood-brain barrier	1:1000 risk of progressive multifocal leukoencephalopathy	HIV-positive status or other immunodeficiency	C

SC = subcutaneous; LFT = liver function test; T_H1 = helper T cell type 1; T_H2 = helper T cell type 2.

KEY POINT

- A paucity of data regarding the long-term safety of the disease-modifying therapies in open-label trials beyond 16 years is available.

and are commonly transient in nature. For these reasons, routine blood studies, including a complete blood cell count and liver function tests, are necessary in patients receiving treatment with interferons. In patients who develop abnormal laboratory values, general practice guidelines indicate either dose reduction or suspension before a second attempt at redosing is made. Patients should be counseled to restrict or abstain from alcohol consumption as that can independently cause hepatic injury. The SC preparations of interferon can have associated site reactions and rarely thyroid function abnormalities. In contrast, glatiramer acetate does not require regular blood monitoring. The most common side effects with glatiramer acetate are injection site reactions, bruising, itching, and lipoatrophy. Approximately 10% of patients will develop infrequent episodes of a self-limited idiosyncratic systemic reaction characterized by one or more of the following: chest pain, palpitations, anxiety, dyspnea, urticaria, flushing, and throat constriction that is not cardiopulmonary in nature, and usually develops within 15 minutes of the injection and usually occurs after several months of treatment.

A paucity of data regarding the long-term safety of the DMTs in open-label trials beyond 16 years is available. Two recent articles have raised the issue of a relationship between the development of cancer and the prolonged use of interferon therapy. A population-based study of Israeli patients with MS on glatiramer acetate showed a slightly increased risk of breast cancer.[3,4] Although not statistically significant, this concern warrants further investigation.

The exact mechanisms of the interferon therapies and glatiramer acetate are not known. In general, the injectable DMTs have an anti-inflammatory effect on the immune system, shifting from a proinflammatory state (helper T cell type 1 [T_H1]) to a more anti-inflammatory (helper T cell type 2 [T_H2]) cytokine profile. Earlier clinical trials showed a superior effect of high-dose/high-frequency interferon over lower-dose interferon.[5,6] More recent comparator trials of interferon beta-1b versus glatiramer acetate[7] and interferon beta-1a versus glatiramer acetate[8] showed no significant clinical differences between glatiramer acetate and the high-dose/high-frequency interferons.

SECOND-GENERATION DISEASE-MODIFYING THERAPIES

Natalizumab represents the first second-generation DMT for MS. A selective adhesion molecule inhibitor, natalizumab prevents autoreactive T cells from crossing the blood-brain barrier by blocking the binding of very late antigen-4, which is expressed on all white blood cells except neutrophils, to vascular cell adhesion molecule 1, which is expressed on the surface of vascular endothelium. In the monotherapy pivotal trial of natalizumab, the relative relapse reduction rate was 67% over 2 years compared to placebo.[9] A 42% reduction occurred in sustained disability as measured by the Expanded Disability Status Scale (EDSS) at 3 months and a 54% reduction at 6 months. Both of the aforementioned outcomes were highly statistically significant. Although natalizumab's efficacy relative to placebo is numerically greater than that of the interferons and glatiramer acetate, in the absence of head-to-head comparative data, it is uncertain whether natalizumab has superior efficacy or whether the apparently greater reductions in relapses and disability are due to recruitment of more benign MS patients with less disease activity.[10] Given the intense reduction in the number of gadolinium-enhancing lesions, natalizumab is an attractive drug for use in patients, such as the one in **Case 3-1**, who continue to have enhancing lesions despite the use of an appropriate platform

Case 3-1

A 34-year-old woman was diagnosed with RRMS. Her presenting symptoms were left facial, arm, and chest numbness; left leg weakness; and bladder frequency; all of which resolved over a period of 3 months. MRI of the brain showed multiple areas of abnormal signal change throughout the corpus callosum, posterior fossa, and subcortical white matter that was typical of demyelinating plaques. CSF analysis was consistent with MS. Cervical cord imaging was normal at the time of diagnosis. High-dose interferon therapy was started. Repeat MRI of the brain and cervical cord 1 year later to assess drug efficacy showed a single new lesion of increased signal intensity in the brain and four new spinal cord lesions, all of which were nonenhancing. She remained clinically stable. During that same year, she went off therapy in June and became pregnant in November. Over the next 2 years, after resuming high-dose interferon therapy, she had two episodes of intermittent paresthesias that resolved without additional treatment. During an office visit, she admitted to not taking her injection therapy at least once a week.

The next year, she developed dizziness, tinnitus, and hearing loss. A neuro-otology workup was negative, and the symptoms were attributed to an MS exacerbation. Repeat brain MRI showed one new lesion in the deep white matter but was otherwise unchanged. She was encouraged to consider natalizumab treatment, but she wished to continue with high-dose interferon therapy. Two years later she developed an odd abdominal sensation radiating into her right leg. Brain MRI showed at least four new lesions, three of which enhanced after gadolinium. Because of her continuing relapses, MRI changes, injection fatigue, and noncompliance, natalizumab was started. After 6 months of natalizumab treatment, MRI of the brain was repeated and was stable without any areas of enhancement compared to the prior study.

Comment. This case illustrates an appropriate change to a patient's DMT in the setting of injection fatigue, breakthrough disease on MRI, and persistent relapses.

KEY POINT

- Natalizumab was only studied at a standard dose of 300 mg IV every month; further investigations are underway to determine whether temporary drug discontinuation will reduce the risk of progressive multifocal leukoencephalopathy.

therapy.[11] The initial enthusiasm regarding natalizumab was dampened by the discovery of three cases of progressive multifocal leukoencephalopathy (PML) in the clinical trial population. All three cases were seen in patients on concomitant DMT or immunosuppressive drug (ISD) therapy (two on IM interferon beta-1a and one on azathioprine in a separate trial for Crohn disease). Natalizumab was voluntarily withdrawn from the market in 2005 and reintroduced in 2006, as no cases of PML were detected in the monotherapy trial.[12] Subsequently, as of May 2010, more than 50 cases of PML have occurred in patients on natalizumab monotherapy. The risk of PML rises with duration of exposure to the drug.[13] No standard treatment for PML exists, but it is well known from other disease states that reconstituting the immune system is crucial for good patient outcomes. A recent pharmacokinetic study showed that rapid, high-volume plasma exchange (PLEX) therapy can effectively remove natalizumab from the circulation, desaturate the lymphocytes, and reestablish the trafficking of lymphocytes across the blood-brain barrier within 11 days[14] compared to approximately 90 days for normal drug elimination. Steroids are sometimes added to the regimen to prevent immune reconstitution inflammatory syndrome (IRIS). Natalizumab was only studied as monthly dosing, and further investigations are underway to determine whether temporary drug discontinuation will reduce the risk of PML.

KEY POINT

- At this time, strict guidelines do not exist for clinicians treating patients with MS who become neutralizing antibody positive while on interferon therapy.

NEUTRALIZING ANTIBODIES

One of the thorniest issues in the treatment of MS today is the debate over the importance of neutralizing antibodies (NAbs) with interferon therapy. NAbs by definition have the potential to partially or completely block the intended drug effect. Numerous studies provide evidence to support the view that persistent high titers (greater than 100) of NAbs renders interferon biologically inactive.[15] At this time, strict guidelines do not exist for clinicians treating patients with MS who become NAb positive while on interferon therapy. The controversy continues because of a number of factors that include lack of consensus on the definition of NAb seropositivity; possible reversion to NAb-negative status; variability of testing from laboratory to laboratory; and varying degrees of immunogenicity among the interferon products. The immunogenicity of the interferons in descending order is: SC interferon beta-1b, SC interferon beta-1a, and IM interferon beta-1a.

In contrast, the implication of the presence of NAbs during treatment with natalizumab is more straightforward. If a patient develops persistent NAbs (defined as two positive titers separated by 42 days),[16] then the clinical effect of the drug is similar to placebo. Patients who develop an anaphylactic/anaphylactoid reaction while on natalizumab, most of whom are anti-natalizumab seropositive, should avoid subsequent infusions. The incidence of persistent NAb seropositivity (6%) is lower for natalizumab compared to the high-dose interferons.

CLINICALLY ISOLATED SYNDROME

Clinically isolated syndrome (CIS) is defined as an initial demyelinating event such as optic neuritis, brainstem/cerebellar syndrome, or incomplete transverse myelitis. Longitudinal natural history data support the fact that patients with CIS and an abnormal MRI scan of the brain have an 85% chance of developing clinically definite MS within 10 years.[17] One

Case 3-2

A 30-year-old man presented to the neurology clinic with a 1-month history of pain in his neck associated with left distal upper extremity numbness and tingling. He had no incontinence of bowel/bladder, visual disturbance, lateralized weakness, easy fatigability, or cognitive problems. He could not remember having any of the above symptoms in the past. He initially had seen an orthopedic surgeon, who gave him hydrocodone for the pain and ordered an MRI of the cervical spine.

The patient's past medical history was otherwise unremarkable. His paternal grandmother had a history of MS. He occasionally drank alcohol but did not smoke. His review of systems was unremarkable. His neurologic examination, including detailed sensory examination, was normal.

The MRI scan of the cervical spine showed two lesions in the cervical cord at levels C4-C5 and C6-C7. The cord lesion at C6-C7 demonstrated mild enhancement after the administration of gadolinium. Further diagnostic workup, including MRI of the brain and CSF studies, was ordered. MRI of the brain showed three periventricular lesions that were nonenhancing. His CSF analysis was unremarkable.

Comment. This case provides a good example of a patient who would meet the criteria for recent clinical trials in patients with CIS. Placebo-controlled trials of patients with CIS show a significant delay in the time between the first and second clinical episodes in patients initiated on DMT.

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