ABSTRACT

Neurodegeneration is thought to occur in the early stages of multiple sclerosis (MS) and appears to be progressive, causing axonal damage and a decline in brain volume over time. In an effort to reduce neuronal injury, researchers are increasingly examining potential neuroprotective effects of currently available, as well as investigational, treatments for MS. This discussion focuses on the natural course of neurodegeneration in MS, current challenges related to assessing neurodegeneration, and the available data on current and emerging treatments that target neuroprotection. At this time, most of the available neuroprotection data are in the form of animal studies, with few treatments (e.g., glatiramer acetate) having supporting evidence from human trials. Completion of large-scale human clinical trials is thus necessary in order to define the role of neuroprotection in clinical practice.

that patients with relapsing-remitting MS receiving active treatment (compared to placebo) exhibited significantly less decline in brain volume.4-10 In a study evaluating the effects of glatiramer acetate on chronic black holes in relapsing-remitting MS, 31.4% of patients receiving placebo and 15.6% of patients treated with glatiramer acetate had progression of new T1 lesions into black holes (8 months after lesion appearance).5 In a small pilot MRS study of 18 treatment-naïve patients with relapsing-remitting MS, those treated with glatiramer acetate (vs placebo) for 2 years experienced a significant increase in the NAA/Cr ratio (10.7% in the large central brain, 7.1% in normal-appearing white matter).11

Monoclonal antibodies offer a more potent, molecular-targeted approach to modifying the course of MS, and of those, natalizumab is purported to have the majority of available neuroprotection data. With respect to its effects on chronic black holes, natalizumab has been shown to significantly decrease the proportion of relapsing MS patients with new gadolinium-enhancing (Gd+) lesions that evolved into T1-hypointense lesions (ie, black holes), proportion of patients who developed large T1-hypointense lesions, proportion of new Gd+ lesions that became T1 hypointense, and the mean per-patient proportion of new Gd+ lesions that converted to T1-hypointense lesions.12 Natalizumab was also associat-

**Table. Disease-Modifying Drugs and Neuroprotection**

<table>
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<th>No Data Available</th>
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<td>Laquinimod</td>
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CNS = central nervous system; IFN = interferon.

**Figure. Pattern of Neurodegeneration in MS**

MS = multiple sclerosis.

THERAPIES TARGETING NEUROPROTECTION

The Table includes disease-modifying drugs with supporting evidence for neuroprotective effects and agents with no available data. Glatiramer acetate is thought to exert neuroprotective effects by increasing production of neurotropic factors, which rescue injured neurons and induce regeneration.7 Available on the market for approximately 10 years, glatiramer acetate has considerable neuroprotection evidence encompassing brain atrophy, black hole, and MRS data. Three trials (ranging from 24 months to 6.7 years) examined the effects of glatiramer acetate on brain atrophy, and found
ed with a significant decrease in brain atrophy after 2 years of treatment.13

EMERGING TREATMENTS

Several investigational agents (eg, fingolimod, laquinimod, BG00012, sodium channel blockers, and glutamate antagonists) may also exert potential neuroprotective effects. Fingolimod (FTY720) is an orally administered sphingosine-1-phosphate receptor agonist that reduces the number of inflammatory T cells in the circulation and in the CNS, ultimately reducing the potential for nerve cell damage.14 Because this agent is very lipophilic, it is able to cross the BBB and exerts effects directly on resident cells within the CNS.14 Thus far, animal studies with fingolimod indicate an overall neuroprotective effect (mediated in part by its actions within the CNS) and human studies are currently under way. The primary concern with fingolimod is its adverse-effect profile, which includes nasopharyngitis, dyspnea, headache, diarrhea, nausea, increases in alanine transferase, lymphopenia, opportunistic infections, and malignancies.15 Bradycardia and atrioventricular block have occurred during the first dose only, and did require hospitalization for some patients in clinical trials.

Laquinimod (ABR-215062) is another orally administered investigational agent that, in animal models of MS, has been shown to decrease leukocyte infiltration into the CNS and to induce a shift from T-helper type 1 (Th1; proinflammatory) cells to Th2/3 (anti-inflammatory) cells.14 Currently, there are no data on the potential of laquinimod to exert neuroprotective effects, but the agent has been shown in phase III clinical trials to have significant activity (as shown on MRI measures) against the relapsing form of MS.19 The agent also appears to exhibit synergistic immunomodulating effects when given with interferon therapy.14 Thus far, laquinimod's adverse-effect profile appears favorable, with reversible dose-dependent liver enzyme elevations being the only significant concern.16,17

BG00012 (dimethyl fumarate) is another oral formulation and is known to activate the Nrf2 (NF-E2 related factor) pathway, which may have a dual neuroprotective and anti-inflammatory effect.18 In a phase IIb trial, doses of 240 mg (3 times daily) significantly decreased the total number of Gd+ lesions in patients with MS.19 The most common adverse events included gastrointestinal symptoms and flushing, the latter of which may initially be severe (lasting for 2 hours after administration of each dose), but should subside after approximately 6 weeks of treatment.20

Sodium channel blockers, which include drugs (eg, phenytoin, flecainide, and lamotrigine) that are already approved for seizures and other indications, have shown promise in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Sodium channel blockers are thought to play a vital role in how nerve fibers transmit signals.20 These agents block sustained sodium influx into nerves, which, when otherwise unopposed, leads to calcium ion influx, resulting in axonal damage.20 In EAE, a 28- to 30-day treatment regimen with oral phenytoin was shown to decrease the loss of axons within the CNS from 63% to 28%.21,22 Flecainide (also given for 28–30 days) was shown to decrease axonal degeneration in EAE from 40% to 17%.23,24 Lamotrigine (given for 27–29 days) reduced the degree of axonal degeneration in EAE from 33.5% to 10.4%.25 With regard to adverse effects, these agents may cause impairment of neuronal signaling, plasticity, and potential problems with withdrawal (eg, clinical worsening and increased inflammation in the CNS).26

Another therapeutic class that may have a potential role in MS are glutamate antagonists, which have sparked an interest based on evidence indicating an excess of glutamate in patients with MS.27,28 Glutamate is normally involved in transmitting signals from one nerve to another, but in excess, this excitatory neurotransmitter may be toxic, leading to a loss of nerve fibers.27 Based on animal studies indicating that a reduction in glutamate levels may protect nerve fibers, 2 glutamate antagonists (memantine and riluzole) are currently being examined as potential treatments for MS.24 Riluzole, which stabilizes sodium channels and inhibits release of glutamate, is currently approved for amyotrophic lateral sclerosis and has been shown to reduce the rate of cervical cord atrophy and development of T1 brain lesions in a pilot trial of patients with primary progressive MS.4,29 A study exploring riluzole in relapsing-remitting MS is currently in the recruiting stages.

CONCLUSIONS

Degeneration of axons is thought to occur progressively, from the onset of MS, and contributes significantly to the theory of neurodegeneration as one of the primary destructive processes in this disease. As such, researchers are increasingly examining various mechanisms of neurodegeneration and identifying potential
molecular targets for therapeutic intervention to prevent neuronal injury. Although current therapeutic data on neuroprotection appear promising, it remains preliminary, with large-scale human trials and well-examined adverse-effect profiles yet to be attained.

REFERENCES