ABSTRACT

Axonal degeneration and central nervous system (CNS) atrophy are common in patients with multiple sclerosis (MS). Clinical and experimental studies have described many pathophysiologic mechanisms that may be important in the development of MS, including the activity of immune cells, inflammatory mediators, neurotransmitters, and intracellular signaling pathways. Clinical trials have only recently begun to evaluate whether medications that target these pathophysiologic processes can slow the progression of CNS atrophy or improve clinical outcomes in patients with MS. Magnetic resonance imaging studies have found that some immunomodulatory therapies improve functional status and slow the rate of CNS atrophy in patients with MS. Other treatments do not appear to slow the progression of atrophy and may actually exacerbate atrophy when administered at high doses. Clinical trials being planned will soon begin to evaluate the neuroprotective effects of sodium-channel or calcium-channel blockade and of combining several different neuroprotective approaches. Future clinical trials may examine ways to restore CNS function after neurodegeneration, perhaps by manipulating gene expression of neurons or glia or providing growth factors that regulate neuronal survival.

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NEUROPROTECTION IN MS: FROM CURRENT THERAPIES TO THE DESIGN OF FUTURE CLINICAL STUDIES

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Despite the importance of inflammatory processes in the pathogenesis of multiple sclerosis (MS), clinical trials of immunomodulating agents in MS have generally been disappointing as many of the available agents appear to have little effect on disease progression. Some medications have been shown to improve magnetic resonance imaging (MRI) outcomes on more sensitive clinical rating instruments such as the Multiple Sclerosis Functional Composite (MSFC) scale, although even these agents have generally been more effective in the early course of the disease. One of the most disturbing features of MS is that the rate at which functional status decreases in patients with progressive disease after an Expanded Disability Status Scale (EDSS) of 4.0 is reached is generally consistent from patient to patient and is largely independent of the preceding course of illness. Although the time that patients spend with relapsing-remitting MS (RRMS) varies considerably, most patients exhibit a decline in EDSS score from 4 to 6 over a period of approximately 5 to 6 years, regardless of whether the initial onset of disease was relapsing or progressive and regardless of the time that elapsed between initial diagnosis and the assignment of an EDSS score of 4.1 This suggests the possibility that the early relapsing and remitting course of the disorder is caused by the exacerbation and resolution of inflammation but that the emergence of progressive disease reflects a process of irreversible neurodegeneration.

Neurodegeneration in patients with MS has been described in several recent clinical studies that used MRI techniques to evaluate the progression of CNS atrophy. Some studies have found that treatments that improve the functional status of patients with MS also reduce the progression of atrophy, although this has not been demonstrated with all medications. In a large
clinical trial that examined the efficacy and safety of interferon (IFN)-beta-1a (Avonex), Rudick et al demonstrated that treatment reduced brain atrophy by an average of 55% in patients with RRMS compared with placebo after 2 years. The effect of treatment on the progression of atrophy emerged only during the second year of the study. Data from the European Cooperative Study reported that the effect of IFN-beta-1a on atrophy also continues into the third year of treatment. In a study of serial MRI cerebral volume measurements in patients with progressive MS who were treated with IFN-beta-1a or placebo for up to 36 months, IFN therapy produced a trend toward reduced atrophy compared with baseline, although the difference between the IFN and placebo groups was not statistically significant (Figure 1). With Rebif, the situation is somewhat more complicated. An analysis of MRI scans of patients enrolled in the Prevention of Relapses and Disability by IFN-beta-1a Rebif Subcutaneously in MS (PRISMS) clinical trial, which compared Rebif 22 µg versus placebo, surprisingly found no significant benefit of Rebif treatment on cerebral atrophy. Patients who received high-dose Rebif (44 µg) exhibited a worsening of atrophy compared with patients treated with placebo. Similarly, a study of spinal cord atrophy found that patients who received Rebif tended to exhibit more atrophy of the upper cervical spinal cord compared with those treated with placebo after 4 years, although this difference was not statistically significant.

Similar observations indicating a trend toward reduced atrophy have been noted in a study of the immune-modulating agent glatiramer acetate (Copaxone), which did not significantly reduce atrophy in patients with RRMS (Figure 2). In a study of whole-brain volume measurements in patients who were treated with cladribine, which promotes cell death in lymphocytes and monocytes, low-dose cladribine and placebo produced similar degrees of atrophy (with losses of brain volume of 0.4% in both groups after 1 year), whereas atrophy tended to be more extensive in patients treated with a higher cladribine dose (1.5%; not statistically significant).

Together, these findings raise the possibility that some—but not all—anti-inflammatory therapies may reduce the progression of atrophy in patients with MS. Over the long-term course of therapy, it may sometimes be necessary to balance the anti-inflammatory effectiveness of treatment with the possibility of an increased risk of atrophy later in the course of progressive disease.
TARGETS OF NEUROPROTECTION THERAPY

Several cellular and molecular targets have been identified that could provide the opportunity to improve neuronal survival and function in patients with MS. Anti-inflammatory agents that target specific cell populations, such as CD8+ T-lymphocytes or macrophages, could directly suppress the immune-mediated processes that are thought to trigger MS and could also have beneficial indirect effects, such as reducing the permeability of the blood-brain barrier or suppressing the release of toxic inflammatory mediators (e.g., nitric oxide, tumor necrosis factor-alpha).

Other possible therapeutic approaches include treatments that modify axon function or survival, membrane Na+ channels, the production of toxic enzymes, or the remyelination of axons. It may also be possible to repair injury to the CNS, perhaps by the use of nerve growth factors or by replacing neurons or oligodendrocytes using hematopoietic stem cells.

PREVENTING INJURY

Animal models and in vitro experimental systems have suggested several possible methods by which neurodegeneration could be prevented. Considerable research suggests that Na+ channels are important in the pathophysiologic processes that produce neurodegeneration in model systems that resemble MS (see article by Dr Stys). Agents that may reduce injury by means of their effects on Na+ channels include anticonvulsants and some antiarrhythmics (e.g., mexiletine). Increased cytoplasmic Ca2+ concentration has also been shown to be important in many models of nerve injury, which suggests that calcium-channel blockers may help to reduce neurodegeneration in MS. Drugs that target other aspects of Ca2+ regulation, such as the Na+/Ca2+ exchanger, are interesting from a theoretical perspective but may be limited clinically by toxic effects, particularly effects on heart function. Other potential approaches to prevent nerve injury include drugs that prevent the release of intracellular Ca2+ stores via ryanodine receptors or that act at central gamma-aminobutyric acid (GABA) receptors.

Several anticonvulsants have been proposed as potential therapeutic agents to reduce neurologic injury. Topiramate, which is being evaluated in clinical trials of patients with MS, blocks the entry of Na+ into neurons; it also inhibits carbonic anhydrase as well as AMPA and kainate receptor signal transduction, potentiates the effects of GABA receptors, and opens neuronal K+ channels. Zonisamide blocks voltage-gated Na+ channels and scavenges hydroxyl radicals and nitric oxide, which are important in the cascade of events that culminate in neuron injury. Lamotrigine inhibits glutamate release and the entry of Na+ through Na+ channels.

Another agent that may prevent neurologic injury is minocycline, an inhibitor of matrix metalloproteinases (MMPs). Minocycline is particularly effective at inhibiting MMP-2 and MMP-9, which are thought to be important in the progression of MS. It also reduces reactive microgliosis, prevents apoptotic cell death, and suppresses the production of inducible nitric oxide synthase and other inflammatory mediators. Minocycline has been shown to reduce neurologic injury in experimental autoimmune encephalitis, an animal model of MS, and is being evaluated in clinical trials of patients with MS.

Glutamate toxicity is also an important mediator of neurologic injury in many clinical settings and may be important in the pathogenesis of MS (see article by Dr Raine). The concentration of glutamate in MS lesions was examined using magnetic resonance spectroscopy in a study of 79 patients with MS. The concentration of glutamate was somewhat elevated in normal-appearing white matter and T1- and T2-weighted images compared with the white matter of healthy control patients, but this difference was not statistically significant. The glutamate concentration within gadolinium-enhanced MS lesions was significantly greater but there was no difference in lesion glutamate concentration between patients with RRMS and secondary progressive MS (SPMS). Glutamate concentration was significantly correlated with duration of disease, EDSS scores, and a specific marker of neuronal injury (N-acetyl-aspartate concentration). The importance of glutamate in the neurologic injury of MS is also suggested by the finding that the glutamate inhibitor riluzole prevented the development of spinal cord atrophy in a pilot study of 16 patients with primary progressive MS. Riluzole inhibits glutamate release, inactivates voltage-dependent Na+ channels, and inhibits the transduction of excitatory amino acid signals. During the first year, when no specific treatment was administered, the average spinal cord cross-sectional area decreased by 2.0%. During the second year, when patients were treated with riluzole, the rate of progression of atrophy decreased, with a mean loss of 0.2%. It may also be possible to improve clinical outcomes by combining immunosuppressive and neuroprotective treatments. Combination treatment was
recently studied in an experimental animal model of amyotrophic lateral sclerosis, in which mice with a genetic mutation that causes the overproduction of the enzyme superoxide dismutase developed gradual neurodegeneration. These investigators examined combination therapy with agents that individually have modest neuroprotective effects: minocycline, riluzole, and nimodipine. Combination therapy significantly delayed the onset of muscle weakness and increased the average lifespan of the animals (Figure 3). This study suggests a combination neuroprotective strategy could increase neuron survival and improve clinical outcomes. One obstacle to applying this approach to clinical research is that combination treatment studies often require large numbers of patients to demonstrate statistically significant differences between treatment groups. A double-blind clinical trial is currently being planned that will examine combination treatment with IFN-beta-1a and topiramate in patients with RRMS who have not previously been treated with immunomodulating drugs. The primary endpoint will be the safety of treatment after 24 months. Secondary outcomes will include measures of brain atrophy, other imaging measures, and clinical outcomes (EDSS, MSFC).

**Promoting Recovery**

It may be possible to promote the recovery of injured neurons by altering the expression of genes that are important in regulating neuronal survival. For example, a gene mutation has been identified in rats (overexpression of the WldS gene) that appears to confer long-lasting protection from axonal injury. Transected axons in these animals remain capable of propagating action potentials for several days.

Nerve growth factors may provide another tool to improve neuronal recovery. Some evidence suggests that brain-derived neurotrophic factor (BDNF) may be of particular interest in MS. BDNF is probably important in the developing nervous system, and studies have shown that it ameliorates neuronal loss in animal models of spinal cord injury and repair (see article by Dr. Murray). BDNF is secreted by T-lymphocytes, B-lymphocytes, and monocytes. The expression of BDNF is increased in patients with RRMS but decreased in those with SPMS, suggesting it may have a specific effect on the regulation of the interaction between immune cells and neurons that could be beneficial as a treatment for MS.

**Summary and Conclusions**

Until recently, relatively few patients had been enrolled in clinical trials to evaluate neuroprotective strategies in patients with MS. Clinical researchers are beginning to consider pragmatic issues in designing studies of neuroprotection as the results of several recent laboratory studies have suggested that it may be possible to slow or even to reverse the progression of neurologic injury in MS. Studies of immunomodulating agents have generally not produced large improvements in CNS atrophy, although some data suggest that IFN-beta-1a may reduce the rate of progression of atrophy in the second year of treatment. Several other neuroprotective strategies, including blockade of Na+ channels, glutamate receptors, or combination treatment approaches, will soon be evaluated in controlled clinical trials.
REFERENCES


