EMERGING TREATMENTS ON THE HORIZON: ANTI-INFLAMMATORY AND NEUROPROTECTIVE THERAPIES FOR MS*

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ABSTRACT

Current options for the treatment of multiple sclerosis (MS) possess important limitations. First-line disease-modifying agents (interferon β-1a, interferon β-1b, and glatiramer acetate) reduce the rate of relapse by only approximately 30%, require parenteral administration, and can cause adverse effects that are difficult for patients to tolerate. Second-line agents (natalizumab and mitoxantrone) are effective for some patients who do not respond to first-line therapies, but are associated with potentially serious safety concerns. Recent research has suggested several promising new approaches to the treatment of MS, and many novel therapies are now being evaluated in randomized controlled clinical trials. T-cell vaccines use the patient's own myelin-reactive cells to stimulate an immune response against self-reactive T lymphocytes, thereby reducing central nervous system inflammation and demyelination. The synthetic peptide MBP8298 resembles a portion of myelin basic protein and suppresses autoantibody formation. Monoclonal antibodies that target several cell-surface molecules have demonstrated considerable effectiveness in patients with MS, but also produce potentially significant immune-mediated adverse effects. Several oral immunomodulatory compounds are being tested in MS clinical trials, including FTY720 (fingolimod), teriflunomide, laquinimid, cladribine, and fumaric acid esters. Neuroprotective agents are in earlier stages of clinical development. Potential neuroprotection strategies for MS treatment include antagonists of neuronal glutamate and sodium receptors, blockers of inducible nitric oxide or of cell signaling pathways that are important in programmed cell death (eg, calpain and caspases), or restoration of neuronal function with neural stem cell transplantation. (Adv Stud Med. 2008;8(9):322-328)

A s discussed in the previous article by Olaf Stüve, MD, PhD, 6 medications are currently approved for the treatment of multiple sclerosis (MS): 3 formulations of interferon (IFN) β, glatiramer acetate (GA), natalizumab, and mitoxantrone. These agents reduce central nervous system (CNS) inflammation and prevent relapses in patients with relapsing forms of MS. However, several significant unmet needs remain in MS therapy. All of the first-line medications (IFNβ-1a, IFNβ-1b, and GA) reduce relapse rates by approximately 30%. In addition, these treatments all require subcutaneous or intramuscular injection at intervals from once weekly to daily, and are associated with adverse effects that can be difficult for patients to tolerate (eg, flu-like symptoms and skin reactions). Natalizumab may produce a greater reduction in relapse rate than first-line thera-

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pies, but is associated with progressive multifocal leukoencephalopathy (PML), a potentially fatal opportunistic infection of the CNS, in approximately 1 of 1000 patients who are treated for 2 years. Mitoxantrone is associated with an increased risk of heart failure, requires careful monitoring of cardiac function, and has also been associated with rare cases of leukemia.

Recent research has examined several potential new strategies for the treatment of MS, including T-cell vaccines, monoclonal antibodies, and oral therapies. Several of these agents are in late stages of clinical testing and may soon become available for the treatment of MS.

**T-Cell Vaccination**

One important mechanism of normal immune function is the inhibition of T-cell activation by regulatory (suppressor) T cells in the peripheral circulation. In MS, a possible defect in the production of suppressor T cells may result in increased activity of myelin-reactive T cells and the formation of inflammatory CNS lesions. One potential strategy for the treatment of MS is therefore to increase the number of suppressor T cells. Just as attenuated microorganisms are used to stimulate protective immunity against infection, irradiated autologous T cells are unable to replicate, but stimulate the production of regulatory T cells against circulating myelin-reactive T cells. This approach has been shown to reduce CNS demyelination in several studies using animal models of MS, and is currently being evaluated in a phase II clinical trial.

**MBP8298**

MBP8298, a synthetic peptide resembling a portion of myelin basic protein, has been designed as a potential treatment for progressive forms of MS. The development of MBP8298 for MS was based in part on the results of studies demonstrating that autoantibodies against myelin basic protein are detectable in cerebrospinal fluid samples from patients with relapsing-remitting MS (RRMS) only during relapses, but are detectable continuously at elevated levels in patients with primary progressive MS or secondary progressive MS. These investigators hypothesized that the suppression of autoantibodies might provide a treatment strategy for progressive forms of MS. MBP8298 induces antigen-specific tolerance by providing a high dose of soluble antigen, resulting in marked suppression of autoantibody formation in patients with progressive MS. In a phase II clinical trial of patients with progressive MS, treatment with MBP8298 once every 6 months did not significantly slow the progression of MS disability. However, when the investigators classified the patients according to human leukocyte antigen (HLA) haplotype, a significant response to treatment was noted for those with HLA-DR2 or DR4. These HLAs are found in a much higher percentage of patients with MS (approximately 60%–70%) than among the general population (approximately 20%–30%), and may be important in the development of autoimmunity in individuals with MS. For the subgroup of patients with HLA-DR2 or DR4 haplotypes, the median time to progression of disability was 78 months for patients who received MBP8298 versus 18 months for patients in the placebo group ($P = .004$; Figure 1). There are 2 large phase III trials currently under way in patients with secondary progressive MS.

**Monoclonal Antibodies**

Daclizumab is a monoclonal antibody that binds to cell-surface receptors for interleukin (IL)-2, a pro-inflammatory cytokine that promotes T-cell proliferation and differentiation. In addition to blocking the effects of IL-2, daclizumab also stimulates the proliferation of CD56+ natural killer cells, which results in a decreased number of circulating CD4+ and CD8+ T cells. In a recent phase II clinical trial of patients with continued MS relapses despite IFN therapy, daclizumab improved several outcomes, including new and total contrast-enhancing lesions, ambulation, and disability. Adverse effects that have been associated with daclizumab include nausea, diarrhea, and metabolic or nutritional disorders (eg, hyperglycemia).

Rituximab is a chimeric human/murine monoclonal antibody that binds to the CD20 cell-surface marker on B cells. Binding of rituximab to CD20 results in the depletion of mature B cells, but not plasma cells, by a complement-mediated process or by direct cell lysis. A related monoclonal antibody—ocrelizumab—also...
binds to CD20 and depletes B cells, but is a humanized antibody that may be less likely than rituximab to cause immunogenic or infusion reactions.\textsuperscript{20} In phase I and phase II clinical trials of patients with MS, rituximab reduced the mean number of gadolinium (Gd)-enhancing lesions by approximately 90% compared with placebo \((P < .001)\) and reduced the relapse rate by 58% \((P = .0238)\).\textsuperscript{21} Rituximab did not reach its primary end point in a recent phase II/III clinical trial of 439 patients with primary progressive MS.\textsuperscript{22} Two cases of PML have been reported in patients with systemic lupus erythematosus who were treated with rituximab.\textsuperscript{23} These patients had been extensively treated with cytotoxic chemotherapy, which is also associated with an increased risk of PML.\textsuperscript{24} Thus, the risk of PML in patients who receive rituximab for MS is not well established. Further studies with ocrelizumab are under way in RRMS.

Alemtuzumab is a humanized monoclonal antibody against the CD52 cell-surface marker that triggers rapid complement-mediated destruction of T cells and B cells.\textsuperscript{25} T cells recover over a period of approximately 16 months; B cells recover within a period of approximately 3 months and may exceed baseline cell counts after 6 months.\textsuperscript{26} Alemtuzumab is administered as a 5-day intravenous infusion once per year. In a phase II clinical trial, 334 patients were randomized to treatment with IFN\(\beta\)-1a subcutaneous or to 1 of 2 doses of alemtuzumab \((12\) or \(24\) mg/day for 5 days).\textsuperscript{27} After 2 years, the risk of relapse was approximately 75% lower with alemtuzumab than with IFN\(\beta\)-1a \((P < .0328)\), and the risk of clinically significant disability was approximately 65% lower with alemtuzumab \((P < .01194)\). This represents a marked reduction in MS activity compared with an established treatment, possibly surpassing any other therapy tested so far. However, clinical studies also have identified potentially significant safety concerns with alemtuzumab, including increased risk of autoimmune disorders (eg, Graves’ disease and Goodpasture’s syndrome).\textsuperscript{28} Idiopathic thrombocytopenia purpura occurred in approximately 3% of patients treated with alemtuzumab in the phase II clinical trial described previously, resulting in 1 fatality.\textsuperscript{29}

**ORAL COMPOUNDS**

T and B lymphocytes require a specific cell-surface receptor (sphingosine-1-phosphate \([\text{S1P}]\)) to exit the lymph nodes and enter the circulation.\textsuperscript{29} FTY720 (fingolimod) is a T lymphocyte S1P receptor agonist that causes T cells to internalize S1P receptors, thereby preventing T-cell egress from the lymph nodes and inducing T-cell apoptosis.\textsuperscript{29} FTY720 does not affect memory T cells that are already resident in tissues.\textsuperscript{30} A phase II clinical trial examined the safety and efficacy of FTY720 at doses of 1.25 or 5 mg for up to 6 months.\textsuperscript{31} Compared with placebo, FTY720 reduced MS clinical activity by more than 50% and reduced magnetic resonance imaging (MRI) evidence of disease activity by up to 80% (Figure 2). In an extension study, patients who initially received placebo exhibited marked reduction in disease activity after they were crossed over to FTY720.\textsuperscript{32} Common adverse events associated with FTY720 treatment included upper respiratory tract infection, diarrhea, nausea, headache, transaminitis, and leukopenia. Potentially serious adverse events included bradycardia, benign arrhythmia, and restrictive pulmonary function.\textsuperscript{31,32}

The pyrimidine synthesis inhibitor teriflunomide blocks the replication of rapidly dividing cells, including lymphocytes.\textsuperscript{33} In a phase II, 36-week, placebo-controlled clinical trial of 179 patients with RRMS,
active MRI lesions were reduced by 61% with low-dose teriflunomide and 64% with high-dose teriflunomide, in comparison with placebo (Figure 3). Adverse events associated with teriflunomide included alopecia, upper respiratory tract infection, and nausea.

Laquinimod is an orally active synthetic immunoregulator that has been shown to reduce neurologic damage in animal MS models. Laquinimod was developed from a predecessor compound (roquimex) that reduced MS activity in some clinical studies but that was associated with potentially serious adverse events, such as pericarditis, myocardial infarction, and pulmonary embolism. In a phase II clinical trial, laquinimod was associated with a 44% reduction in the number of active MRI lesions after 24 months.

Cladribine is an oral agent that is in late-phase clinical testing for MS. Cladribine was designed to exploit the process by which T lymphocytes enzymatically degrade deoxynucleotides. These cells are unique in that they use only a single enzyme—adenosine deaminase—to degrade the deoxynucleotide deoxyadenosine, whereas other cells also use a second enzymatic pathway. Cladribine is an analogue of deoxyadenosine that is resistant to degradation by adenosine deaminase. Cladribine treatment results in the accumulation of deoxyadenosine and the selective depletion of T cells (especially CD4 T cells). Cladribine has been fast-tracked by the US Food and Drug Administration and is currently being evaluated in a phase III clinical trial.

Oral fumaric acid esters have been used for decades in Germany for the treatment of psoriasis. Although the precise mechanism of action is unknown, fumarates induce immune deviation of T cells from a helper T cell (Th1) 1 (pro-inflammatory) to a Th2 (anti-inflammatory) profile. In a phase I clinical trial, treatment with oral fumarate for 6 months produced a 69% reduction in the number of Gd-enhancing lesions, a 48% reduction in T2 lesions, and a 32% reduction in relapses, compared with placebo. Adverse events with oral fumarate have included gastrointestinal symptoms (eg, cramps and diarrhea), flushing, transaminitis, and upper respiratory tract infection.

**Neuroprotection Strategies for MS Treatment**

None of the currently approved MS treatments act primarily by neuroprotective effects. Neuronal death occurs by several different mechanisms, each of which
provides a potential therapeutic target for the development of new MS therapies.

Glutamate is the principal excitatory neurotransmitter in the mammalian CNS, but is potentially neurotoxic at high concentrations (a phenomenon that has been referred to as excitotoxicity). Several glutamate receptor antagonists have been developed for the treatment of neurodegenerative diseases. Although these agents have generally not been beneficial in the treatment of acute neurologic injury (eg, stroke), the therapeutic window in MS may be longer. Orally active inhibitors of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, or AMPA, subtype of glutamate receptor have been shown to reduce neurologic injury in animal models of MS. These findings do not appear to be related to alterations in inflammation or immune function, and may therefore represent specific neuroprotective effects.

Sodium channel blockers reduce electrical activity across neuronal membranes and may also reduce the likelihood of neurodegeneration. Flecainide is a sodium channel blocker that has produced significant protection of axons in animal models of inflammatory CNS injury and MS. Axonal protection in animal MS models has also been noted with some approved antiepileptic agents (eg, lamotrigine and phenytoin). Several other neuroprotective strategies have been proposed, although none has been extensively evaluated in patients with MS. The release of nitric oxide from immune cells has been associated with neuronal injury in MS and other neurodegenerative conditions. Although nitric oxide is therefore an attractive potential target for the treatment of MS, it cannot be blocked directly because it is an important mediator of several physiologic processes, including the maintenance of vascular tone. Specific blockers of an inducible form of nitric oxide within the CNS are being developed for MS therapy. Calpain is a calcium-activated protease that is important in axonal degeneration, and inhibitors of calpain have been shown to prevent neurodegeneration in some animal models (eg, in response to crush injury of the optic nerve). Other potential neuroprotective strategies include neurotrophic factors (eg, nerve growth factor, brain-derived neurotrophic factor, and neutrophin-3), strategies to block caspases (which are specific mediators of apoptosis), or the use of neural stem cell transplantation to promote remyelination or regeneration of neurons.

**CONCLUSIONS**

Better understanding of the role of the immune system in the pathogenesis of MS has led to the recent development of many novel treatments. Therapies that target specific immune mechanisms may provide greater efficacy with less risk of serious adverse events than current treatments. Other advances include the development of orally administered agents and parenterally administered medications that require less frequent dosing. Although several investigational agents appear promising for the treatment of MS, all have potentially significant safety or tolerability concerns. Prevention of neurodegeneration or restoration of function are potential treatment strategies for patients with MS, but have been less extensively evaluated.

**QUESTION AND ANSWER SESSION**

Q: How should we define neuroprotection? Should we include outcomes, such as cognition, ambulation, or pain?

Dr Markowitz: My opinion is that ultimately you want to prevent any destruction of CNS tissue. I think that should encompass cognition. It should encompass any objective measures that we have clinically, including walking, Expanded Disability Status Scale, MRI, or any sort of neurologic testing that we do currently. I think MRI gives us the advantage of looking at changes we cannot see clinically, but that are coming in the future.

Dr Stüve: At a molecular or cellular level, I think neuroprotection is whatever prevents neurodegeneration. There is good evidence from the talks that we have heard today that there is neurodegeneration in MS. But even neuroscientists and neurologists who are really experts in neurodegenerative diseases do not know exactly what constitutes neuroprotection.

This raises a question that I have about new therapies. We are about to enter a very exciting and interesting time, and the quantity and quality of therapeutics that are going to enter the market in the next 5 years is staggering. But we are going to be faced with one resounding question. We have 4 therapies that have been on the market for between 12 and 20 years, with what I would argue are very good safety profiles. We do not have any deaths, cancers, and so on, with any of the injectable drugs. We are going to be faced with drugs...
that may be better in terms of efficacy, but they all have safety concerns, and the concerns are different for each drug. How do we weigh these issues with these new treatments? Will we switch to these new therapies as soon as they become available?

**Dr Markowitz:** I struggle with this issue because I have enrolled patients into clinical trials with these compounds, and I have had to address these safety issues. I think that the MS community has become very comfortable with the current therapies, and they like the safety profiles of these agents. But there is increasing awareness that we need to be a little bit more aggressive with our therapies in the future where we have a potential for better efficacy that can really shut down the disease and prevent the long-term disability issues with some, but significant, risk. I think we will take on more risk as time goes on, because we will see the benefit of doing that. I think the field will change. When you have 5 compounds that are all putting you at a 50% to 60% reduction in relapses, that really is better than what we have used to date. Some of the drugs may get up to 70%, or they may really slow disability progression. You will choose that, but you will figure out a way to monitor for these safety issues so that patients can safely take it.

**REFERENCES**

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