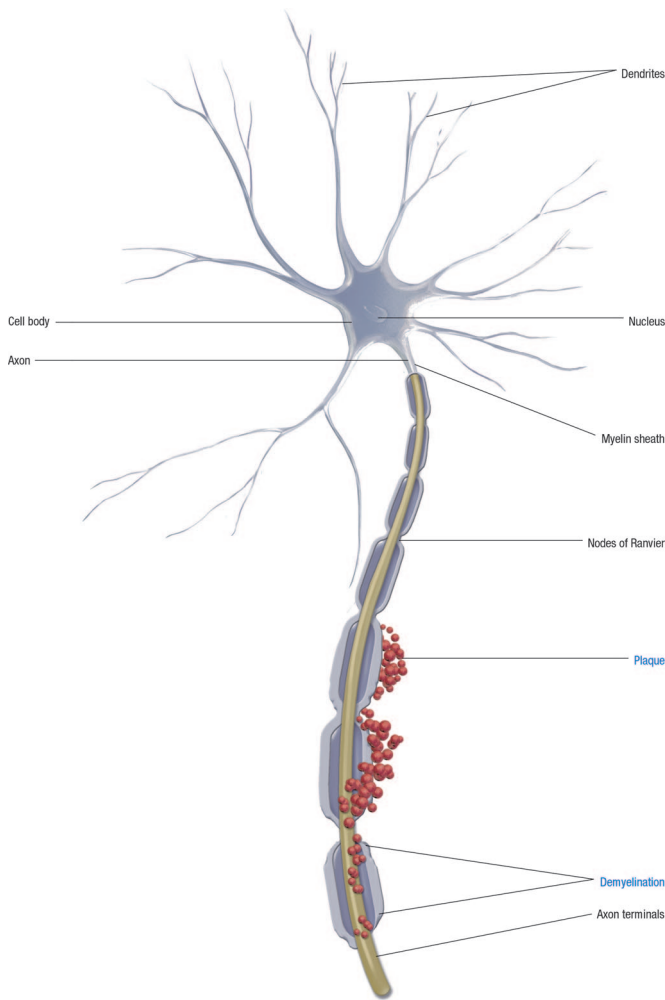


Therapeutic options in multiple sclerosis

Five new things



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Neurology[®] Clinical Practice
2010;75(Suppl 1):S22–S27

Care of the patient with multiple sclerosis (MS) is becoming increasingly complex, with new symptomatic therapies (e.g., dalfampridine), enhanced use of disease-modifying therapies that are potentially both more efficacious and more risky (e.g., natalizumab, rituximab) than “standard” immunomodulators, the advent of oral disease-modifying therapies (DMTs) (e.g., fingolimod, cladribine, teriflunomide, laquinimod), and the possibility of regenerative or reparative therapies (e.g., stem cells, neuroprogenitor cells, antibodies to leucine-rich repeat and immunoglobulin (Ig) domain containing NOGO receptor interacting protein-1, i.e., anti-LINGO therapies). All of this is happening in the context of a suggestion that MS may fundamentally result from aberrant venous flow, so-called chronic cerebrospinal venous insufficiency (CCSVI), and a similarly fundamental pathologic discussion of the relationship between inflammation and degeneration over time in patients with MS. Noting the difficulty of choosing among many options, we present discussions of 5 new topics relevant to patients with MS and their neurologists in 2010.

NEURAL REPAIR AND REGENERATION Although a significant number of patients treated with natalizumab might undergo some improvement in quality of life,¹ in general the Food and Drug Administration (FDA)–approved DMTs aim for stability and lack of disease progression as major outcomes. In addition, all the FDA-approved DMTs essentially work by altering the immune system, with so-called immunomodulation, selective immunosuppression or immune deletion, or more general immunosuppression. Given the large number of patients with MS with fixed or worsening neurologic deficits, and the apparent lack of efficacy of presently available medications to alter the fundamental nature of primary progressive and secondary progressive MS, approaches which provide significant neuroprotection, enhance neural repair, or provide cells for neural regeneration are sorely needed.

Leucine-rich repeat and Ig domain containing NOGO receptor interacting protein-1 (LINGO-1) is a transmembrane protein selectively expressed on brain and spinal cord neurons and oligodendrocytes. It inhibits axon out-

sprouting as well as differentiation of oligodendrocyte precursor cells (OPCs) into functional oligodendrocytes capable of myelinating CNS nerves. In multiple experimental allergic encephalomyelitis (EAE) models of MS, either mice which have had LINGO-1 knocked out of their genetic repertoire or mice treated with an anti-LINGO monoclonal antibody have significantly less clinical EAE disease as well axonal and myelin damage pathologically.² This improvement is associated with significant enhancement of OPCs developing into functioning oligodendrocytes.³ Phase I studies are now underway with an anti-LINGO-1 monoclonal antibody in patients with MS.

Although autologous stem cell reimplantation as part of high-dose immunoblation therapy has been studied for many years in MS and other possible autoimmune disorders, this approach has been more focused on “rebooting” of the immune system, and not neuroprotection or primary neural repair. Open-label, nonrandomized studies of patients with MS treated in this fashion have shown stability in patients with progressive disease.⁴ In a recent publication, Burt et al.⁵ reported 17/21 actively relapsing patients improved by at least 1

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Disclosure: Author disclosures are provided at the end of the article.

point compared to baseline score on the Extended Disability Status Scale (EDSS) an average of 37 months after treatment. These studies were not designed to understand whether the immunoablation, the stem cell replacement, or some combination of the two resulted in disease stability or improvement. Similar studies are underway in the Ottawa Hospital in Canada.

Both mesenchymal stem cells (whole bone marrow cells with hematopoietic stem cells removed)⁶ and neural progenitor cells^{7,8} have been useful in ameliorating the effects of EAE. Although the mechanisms by which MSC might accomplish this have not been completely worked out, as reviewed by Freedman et al.,³⁵ there are likely effects on immunomodulation (e.g., induction of immune tolerance, inhibition of B-cell responses, conversion of CCL2 from agonist to antagonist of T-cell functions), neuroprotection (e.g., antiapoptosis, antioxidant, release of trophic factors), and true neural repair (e.g., enhances differentiation of OPCs into fully functioning oligodendrocytes). In a recent publication, Rice et al.⁹ reported results in 6 patients with relapsing-progressive MS treated with autologous bone marrow transplant using filtered whole bone marrow cells without expansion or selection, and without prior conditioning or immunoablation. In this phase I study, all 6 patients tolerated the same-day outpatient procedure well, with no adverse effects and no change on brain MRI scan at 3 months. Over 12 months, clinical scores in this small study were either stable (EDSS and Multiple Sclerosis Functional Composite [MSFC]) or slightly improved (Multiple Sclerosis Impact Score 29) compared to baseline, and mildly improved multimodal evoked potentials over 12 months hinted at the possibility of neural repair. Similar studies with mesenchymal stem cells are underway or about to start at Hadassah Hospital in Israel and the Cleveland Clinic in the United States. Studies using OPCs are being planned or considered in patients with amyotrophic lateral sclerosis, spinal cord trauma, and inherited leukodystrophies.

CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY Although MS is viewed by many to be an autoimmune disease, the evidence supporting this concept is elusive.¹⁰ There remains no evidence, for example, that Igs identified within the CSF of patients with MS are directed against any myelin proteins.¹¹ Into this breach comes the theory that MS is fundamentally a disorder of venous backflow in any of several combinations of veins draining the brain and spinal cord. In a series of articles using transcranial color-coded sonography (TCCS), Zamboni et al.¹² in Italy first reported in 2007 that, compared to

60 normal control patients, 89 patients with MS had significantly increased risk of bidirectional flow and/or reflux in deep middle cerebral veins and the transverse sinus. The term CCSVI was coined. They subsequently expanded this approach using TCCS and imaged extracranial veins with echo color Doppler (ECD).¹³ Examining 5 sets of potential venous abnormalities, they reported that having at least 2 of 5 abnormalities correctly distinguished between 65 patients with MS (at least 2 abnormalities in all patients) and 235 controls (0 patients with 2 of 5 abnormalities) with 100% specificity and 100% sensitivity. Venous catheterization of the azygous and internal jugular venous systems appeared to confirm the results in all 65 patients with MS compared to 48 controls. A subsequent 18-month open-label treatment study of balloon angioplasty in these 65 patients reported that, compared to baseline measurements, there was no significant decrease in annual relapse rate, but there was a higher number of patients free of relapses and of gadolinium-enhancing lesions, and quality of life was improved in relapsing-remitting multiple sclerosis (RRMS) on both physical and mental subscales at 6 and 18 months, but only minimally for progressive patients at 6 but not 18 months.¹⁴ Notably, all patients stayed on their DMT, and in nearly 50% of cases, internal jugular veins restenosed after angioplasty. In a podium presentation at the annual Academy of Neurology meeting in Toronto in the spring of 2010, Dr. Zamboni also claimed a significant number of these venous abnormalities appear to be caused by congenital valvular problems in the veins, although the number of inspected cases was not clear.

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Even if accurate, it is unclear if venous abnormalities represent a cause or an effect of MS. In addition, there were a number of methodologic issues raised by these studies, including lack of blinding, use of a single sonographer, lack of verification at other clinic sites, and others.¹⁵ In a press release dated February 9, 2010, after training with Dr. Zamboni, researchers at the University of Buffalo reported 62.5% of 280 patients with MS and 25.9% of 220 controls had at least 1 of the same 5 criteria abnormal (somewhat lower percentages for both groups when using 2 criteria as the cutoff). Thus, they could not reproduce the remarkable 100% sensitivity and specificity

of the Italian group. In addition, a collaboration between the Italian and the Buffalo groups reported significantly lower venous volumes in the intracranial veins of patients with MS compared to controls.¹⁶ It is not immediately apparent, however, how venous backflow would result in lower intracranial venous volumes. In addition, 2 very recent controlled and blinded studies using either MRI (phase contrast and contrast-enhanced)¹⁷ or TCCS¹⁸ failed to confirm either the Italian or Buffalo reports. Finally, the National Multiple Sclerosis Society and Multiple Sclerosis Society of Canada have funded 7 2-year grants to independently assess, using multiple different techniques and control groups, whether the general concept of CCSVI is relevant in MS or not.

BIOMARKERS IN MS A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or pharmacologic responses to a therapeutic intervention. An ideal biomarker should provide accuracy, reproducibility, high sensitivity to detect changes and disease progression, and good correlation with other, validated disease measurements. Identification of markers that could make an accurate MS diagnosis early in the disease process, predict the development of MS in high-risk populations, or predict response to therapy would be extremely helpful.

Although intrathecal IgG synthesis is both a relatively sensitive and specific indicator of demyelination, the presence of oligoclonal bands (OCBs) and IgG synthesis in CSF of patients is not pathognomonic of the disease, and can be found in other inflammatory neurologic diseases.¹⁹ Some studies suggest the presence of IgM oligoclonal bands could be a more specific indicator for the diagnosis of MS and predict a worse clinical course and high relapse rate.²⁰ Intrathecal production of soluble vascular adhesion molecule (sVCAM-1) is elevated in patients with MS and might play a role in predicting the progression from clinically isolated syndrome (CIS) to clinically definite MS.²¹ It has been recently suggested that patients with RRMS have significantly higher CSF levels of α -1 antichymotrypsin (A1AC), α -1 macroglobulin (A2MG), and fibulin 1 as compared to control subjects.²² Another study notes serum IgG antibodies against Epstein-Barr virus nuclear antigen-1 are present during active immune responses in MS, with good correlation with gadolinium-enhancing lesions on MRI.²³

MRI has become an important method for early diagnosis of MS.²⁴ Baseline MRI pattern might also be a strong predictor for accumulation of disability as suggested by the presence of spinal cord, infratentorial, and gadolinium-enhancing lesions seen on early

scans and accumulation of disability 6 years later.²⁵ Nonconventional MRI techniques also show promising results as demonstrated by significantly lower regional magnetization transfer ratio values in patients with CIS and MSFC scores.²⁶ Lower levels of *N*-acetylaspartate and increased levels of myoinositol and creatine in normal-appearing white matter have been seen in patients with CIS, suggesting widespread axonal damage, and correlated with early conversion to clinically definite MS, and poor executive function performance 3 years later.²⁴

Interferon- β (IFN β) is one of the first-line DMTs in MS and significantly reduces clinical and MRI disease activity. However, only half of patients respond well. In a cohort of 26 subjects with RRMS, including 14 IFN β nonresponders, analysis of serum cytokines showed that 6 of the nonresponders had significantly elevated interleukin-17 compared with responders ($p < 0.001$). Nonresponders were defined by the presence of clinical relapses and use of steroids. Other markers including endogenous IFN β production could help predict responsiveness to IFN β .²⁷ Another potential marker of biologic response to interferon therapy is the presence of myxovirus-resistance protein A (MxA), an antiviral protein exclusively induced by type 1 interferons.²⁸ Quantification of MxA expression might be a sensitive measure of IFN β activity.

EFFICACY AND SAFETY OF EMERGING ORAL THERAPIES In the last decade, a new armamentarium of novel and promising neurotherapeutic strategies have been developed and tested in patients with MS. Of those, 2 oral therapies are showing a high level of efficacy, with acceptable safety and tolerability profile, and are under FDA review.

Fingolimod (FTY720), an oral sphingosine-1-phosphate (S1P) analog, is a partial agonist on S1P receptors, thereby blocking the mechanism that allows lymphocytes to migrate out of secondary lymphoid structures.²⁹ Multiple treatment studies in patients with MS have been performed and reported in the last several years.^{29,30} In comparison to weekly IM IFN β 1a, oral fingolimod (0.5 mg daily dose) demonstrated a 52% relative reduction on annualized relapse rate ($p < 0.001$; 95% confidence interval [CI] 0.12–0.21).²⁹ A second study comparing 2 doses of fingolimod (1.25 mg and 0.5 mg) showed similar efficacy with a relative reduction in annualized relapse rate of 60% and 54%, respectively, compared to placebo ($p < 0.001$; 95% CI 0.13–0.19 and 0.15–0.22, respectively).³⁰ In addition, fingolimod also reduced the probability of disability progression at 3 and 6 months over a 24-month period compared to placebo (hazard ratios, 0.68 for the

1.25-mg dose and 0.70 for the 0.5-mg dose). Adverse reactions included bradycardia, nasopharyngitis, dyspnea, headaches, diarrhea, and nausea. Initial bradycardia was seen more frequently in the high-dose group. Three cases of basal cell carcinoma, 3 cases of squamous cell carcinoma, and 1 case of melanoma have been reported. Two fatalities occurred during the trial associated with intracerebral varicella zoster and herpes simplex virus infections. In addition, a single case of hemorrhagic encephalitis was also reported with unclear causal relationship, as was 1 case of fatal, and 1 nonfatal, lymphoma.

Cladribine is a purine nucleoside analog that causes lymphotoxic effects by incorporation into DNA of resting and dividing cells with high deoxycytidine kinase activity (lymphocytes and monocytes), and subsequent interruption on DNA replication, DNA damage, and cell death. In addition to its lymphotoxic effects, cladribine possesses epigenetic properties, by inhibiting S-adenosyl homocysteine hydrolase and DNA methylation. A recent placebo-controlled phase III trial using oral cladribine in patients with RRMS showed a 58% reduction in annualized relapse rates (3.5 mg/kg daily for 4 to 5 days, with 2 courses in the first year) at 2 years compared to placebo. In addition, 80% of the patients remained relapse-free, compared with 61% of the patients in the placebo group ($p < 0.001$ for both dose regimens). Patients in the active drug group experienced a 30% reduction in the risk of disability progression relative to patients in the control group.³¹ Adverse events included headaches, nasopharyngitis, upper respiratory tract infections, and nausea. Lymphopenia occurred more frequently in the active drug group (22%). Of the patients treated with cladribine tablets, 2.3% reported herpes zoster infections, although these were localized to the skin and were responsive to preventative treatment.

Fingolimod is in the final stages of FDA approval process, with expected approval sometime in late summer or early fall 2010, and cladribine is on fast track as of August 2010. These reports highlight the promising efficacy and potential significant risks that accompany these new oral therapies. What role they eventually play in the treatment of newly diagnosed and other patients with MS remains to be seen.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY RISK WITH NATALIZUMAB THERAPY

Natalizumab, a humanized monoclonal antibody that binds to α -4 integrin molecule at the β 1 and β 7 epitopes, prevents extravasation of T and B cells into the CNS, and consequently reduces inflammatory immune reactions in lesions of MS. Therapy with natalizumab has been shown to be highly effective in relapsing forms of MS. However,

natalizumab was associated with progressive multifocal leukoencephalopathy (PML), a rare opportunistic, demyelinating viral infection of the CNS caused by JC virus (JCV), shortly after its approval in 2004, prompting temporary cessation of all use in 2005. Between 50% and 86% of adults have antibodies against JCV, likely due to exposure to the virus during early childhood.³² It has been traditionally thought that JCV remains latent in the bone marrow and kidneys of healthy individuals, and only causes CNS infections under periods of immunosuppression. Recent studies, however, suggest the infection is active during persistence at a basal level, and might be activated by immune dysfunction. In addition, it is possible JCV is already present in the brain of healthy individuals and can undergo reactivation after treatment with immunosuppressants.³³ During treatment with natalizumab, hematopoietic stem cells and pre-B cells are forced to migrate from the bone marrow. Patients with MS who receive natalizumab treatment have an increase in CD34+ cells in their circulation, as well as an upregulation of genes involved in B-cell maturation. This dynamic creates a favorable environment for JCV, which can reside in a latent state in the bone marrow for long periods before the development of PML and which can use B cells and their DNA-binding proteins to initiate viral multiplication.³³ These findings, however, were not supported by recent cross-sectional and longitudinal studies in this large cohort of patients with MS, suggesting no substantial change in the presence of JCV DNA with natalizumab treatment.³⁴

Natalizumab was reintroduced in 2006. As of July 2010, 63 confirmed PML cases have been reported among more than 71,400 patients exposed to natalizumab therapy. Based on those numbers, the overall risk of PML is estimated to be 0.85 per 1,000 patients (95% CI 0.65–1.09 per 1,000 patients). The duration of therapy appears to impact the risk of developing PML, with higher incidence of PML with prolonged duration of treatment. As of August 2010, among patients who had received 25 or more infusions, the incidence of PML increased to 1.39 per 1,000 patients (95% CI 0.98–1.92). In addition, prior use of immunosuppressant drugs is associated with 4-fold higher risk of developing PML. There are 2 clinical trials currently evaluating the presence of anti-JCV antibodies in patients receiving natalizumab therapy, both looking at patients independent of the duration of treatment. Although the ultimate significance of JCV antibody titer as an indicator of PML risk is still unclear, it will be advantageous, if the test performs well, to know the antibody status of patients before initiation and/or during natalizumab therapy.

DISCLOSURE

Dr. Miravalle serves as a consultant for Bayer Schering Pharma, EMD Serono, Inc., Advanced Studies in Medicine (ASiM), and Novartis. Dr. Corboy serves as Editor for *Neurology® Clinical Practice* and as Section Editor for *Neurology Today*; serves as a consultant for Bayer Schering Pharma, EMD Serono, Inc., Advanced Studies in Medicine (ASiM), and Novartis; has received research support from Novartis, BioMS Medical, Orasi Medical Inc., the NIH/NINDS (1UO1NS4571901A1 [PI]), and the National MS Society; and has reviewed files and given expert testimony in medico-legal cases. He is a part-time employee of the Denver Veterans Medical Center.

Received August 19, 2010. Accepted in final form September 3, 2010.

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Neurology 2010;75;S22-S27

DOI 10.1212/WNL.0b013e3181fb3676

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