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Abstracts and Insights From the 2011 European Meeting in MS: Update on New Treatments, Clinical Aspects of MS, and Biomarkers CME

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Goal
The goal of this activity is to discuss recent conference data related to the treatment of MS.

Learning Objectives
Upon completion of this activity, participants will be able to:

1. Evaluate conference data related to both disease-modifying and symptomatic MS therapies, and assess the therapeutic implications of such data
2. Identify factors that may increase the risk for disease progression and serious complications associated with MS therapies
3. Review the role of biomarkers and MRI in appreciating the multifaceted pathophysiology of MS

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Abstracts and Insights From the 2011 European Meeting in MS: Update on New Treatments, Clinical Aspects of MS, and Biomarkers CME

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Introduction

Multiple sclerosis (MS) is a neurodegenerative disease that affects 400,000 people in the United States and more than 2.5 million worldwide.[1] It is generally believed to be an autoimmune disease, and it is the most common cause of nontraumatic neurologic disability in young adults.[2,3] Nearly 2 decades ago, the US Food and Drug Administration (FDA) approval of interferon beta-1b inaugurated the era of injectable disease-modifying therapies. Other injectable interferon-beta preparations and glatiramer acetate followed, and all offered reduced relapse rates with low potential for serious adverse events.

In 2004, the introduction of natalizumab, a monoclonal antibody against alpha4-integrin that is administered by monthly infusion, dramatically decreased relapse rates in many patients. A potentially serious adverse event to consider with this treatment, however, is progressive multifocal leukoencephalopathy (PML). In September 2010, the FDA approved fingolimod, the first oral immunomodulatory therapy. Fingolimod showed increased efficacy compared with interferon beta-1a intramuscularly. Potential adverse events with this agent include novel complications such as first-dose bradycardia, macular edema, and a low risk for severe infections.

At present, several oral drugs are completing phase 3 clinical trials and appear headed for FDA approval based on their efficacy and safety data. These include BG-12 (dimethyl fumarate), laquinimod, and teriflunomide. A new set of injectable therapies, the monoclonal antibodies alemtuzumab, daclizumab, and ocrelizumab, are also demonstrating impressive results on annualized relapse rate and other efficacy measures and require only infrequent administration. Whether the benefits of these new drugs outweigh the adverse events should become apparent in the near future, with increased longitudinal observations and additional clinical trials.

The development of biomarkers that predict response to a particular drug or likelihood of adverse reactions may aid in the s election and monitoring of therapy. The complexities involved in choosing initial therapy may be followed by the clinical dilemma of whether (or when) to switch from one interferon to another, from an interferon to glatiramer acetate (or vice versa), or to another class of therapy (oral, injectable). Published guidance for these critical clinical decisions remains limited.

In addition to disease-modifying therapy, optimal treatment of MS involves the management of symptoms. Decreased walking speed can now be addressed with dalfampridine, a welcome addition to the treatment of MS. Pseudobulbar affect can also be reduced by a dextromethorphan/quinidine combination recently approved by the FDA. Research continues into the pathophysiology of MS, with an expanding appreciation of the importance of grey matter lesions in addition to the characteristic demyelinating white matter plaques.

Highlights in the advancement of therapeutic and symptomatic therapies as well as advances in our understanding of MS pathophysiology from the recent 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS), which was held October 19-22, 2011, in Amsterdam, The Netherlands, are presented below.

What is the greatest barrier to effectively managing symptoms of MS?

- ◯ Treatment-related adverse events
- ◯ Paucity of effective symptomatic treatments
- ◯ Treatment adherence
- ◯ Disease progression

How confident are you in your ability to optimize timing and selection of a new agent when switching therapy?

- ◯ Not confident
- ◯ Somewhat confident
- ◯ Moderately confident
- ◯ Confident
- ◯ Extremely confident

Update on MS Treatments

Comorbidities and Symptomatic Treatment

A group of 25 patients with MS and upper limb tremor entered a double blind, randomized study of 100 IU of onabotulinum toxin A or placebo with treatment crossover at 12 weeks.[4] Onabotulinum toxin A resulted in significant improvement compared with placebo on multiple measures, including Bain scores for tremor severity at 6 weeks (P = .005) and 12 weeks (P = .001), writing at 6 weeks (P = .001) and 12 weeks (P = .003), and drawing at 6 weeks (P = .006) and 12 weeks (P = .002). Postural, "bat-wing," and kinetic tremor also showed significant improvement at 6 and 12 weeks. Weakness after onabotulinum toxin A occurred in 42.2% compared with only 6.1% after placebo (P = .005), but it was not disabling and resolved within 2 weeks.

Data from the Women's Health Initiative[5] that included 449 women with MS and 93,676 women overall revealed that women with MS were more than 4 times as likely to have osteoporosis than were controls (odds ratio [OR] 4.14, P < .001). Women with MS reporting osteoporosis were more likely to be younger and to have smoked cigarettes, and they consumed less calcium from supplements. The issue of osteoporosis is particularly important in people with MS because of the increased risk for falls and subsequent bone fractures.

In a retrospective study of 533 patients,[6] pregabalin and gabapentin were the drugs most commonly used for symptoms such as paresthesia in addition to disease modifying therapies. Patients taking mitoxantrone or those with higher Expanded Disability Status Scale (EDSS) scores were more likely to receive symptomatic therapy.

Dalfampridine was approved in January 2010 to improve walking speed in those with MS. A potassium-channel blocker, it increases conduction of action potentials in demyelinated axons. The usual adult dose is 10 mg twice daily. Dalfampridine is the first drug for symptomatic therapy approved specifically for patients with MS. A post hoc analysis of 343 patients in 2 phase 3 double-blind trials (MS-F203/MS-F204) of extended-release dalfampridine demonstrated that 33% of patients in the dalfampridine group walked at least 20% faster on the timed 25-foot walk compared with 14% in the placebo group (P < .001). Those who walked at least 20% faster had a -8.4-point change in the MS Walking Scale. A change of -6 is an established estimate of clinically meaningful change.[7]

When patients discontinued dalfampridine at the end of the clinical trials, improvement in walking speed was lost, demonstrating that the drug is a symptomatic rather than a disease-modifying agent. A long-term assessment of 132 patients in the MS-F203 extension study and 88 subjects in the MS-F204 extension study revealed that improvements in walking speed returned for up to 3.5 years when patients resumed open-label treatment. Over time, walking speed declined from its peak, possibly as a result of MS progression.[8]

Switching Therapies

Data from 155 patients in the international, noninterventional, longitudinal Coptimize study[9] who switched from any MS drug to glatiramer acetate and were followed for 12 months showed an annualized reduction in relapse rate of 65% (from 0.84 before the switch to 0.29 after the switch; P < .001) and a stable EDSS. To date, 144 clinics in 19 countries have enrolled 637 patients (70.9% women, median age 40) in the Coptimize study, and more data will be forthcoming.

In a study of 10 patients who stopped natalizumab, 4 started treatment with fingolimod within 3-7 months and the other 6 patients stayed off all therapy. After a follow-up of 13 months, all 6 patients off therapy and 1 patient on fingolimod had clinical relapses. The annualized relapse rate of the patients off therapy was 2.7 compared with 0.9 for the patients taking fingolimod.[10]

After treatment with natalizumab for at least 12 months, patients who entered the RESTORE study[11] were randomly assigned to

1 of 3 arms: continue natalizumab for 24 weeks (n = 45), switch to placebo (n = 42), or switch to interferon beta-1a intramuscularly (n = 17), glatiramer acetate (n = 17), or methylprednisolone (n = 54). The first 2 study arms were double blind. At week 24, all patients returned to open-label natalizumab. During the natalizumab discontinuation, MS disease activity (defined as a clinical relapse and/or 1 new Gd+ lesion > 0.8 cm3 in volume or ≥ 2 Gd+ lesions) was seen in 18 patients receiving placebo, in 1 patient receiving interferon beta-1a, in 8 patients receiving glatiramer acetate, and in 21 patients receiving methylprednisone, compared with no patients receiving natalizumab. Monthly methylprednisolone did not suppress disease activity. None of the patients who continued natalizumab had abnormal MRI activity. However, 44% of the placebo patients and 7%-53% of patients on "other" therapy did. Because of the relatively high rate of clinical and MRI relapse in patients who stopped natalizumab, the authors recommended close follow-up and monthly MRI for patients who must switch from natalizumab.

Patients taking natalizumab for 2 years who are positive for JC virus antibodies and who have previously been treated with immunosuppressant therapy are at increased risk for PML developing. Chinea and coworkers[12] at the San Juan MS Center are studying patients who were switched to glatiramer acetate after at least 12 natalizumab infusions. These patients also tested positive for the JC virus antibody and previously received a disease-modifying drug. These researchers are trying to determine whether glatiramer acetate can suppress disease activity.[12] The results are pending.

Long-term Safety

Long-term safety data of teriflunomide, an oral disease-modifying drug in development, were presented[13] from a study that included 147 patients who were followed in a phase 2 open-label study for up to 9 years. The study included 2 groups: patients who received 7 mg of teriflunomide and patients who received 14 mg of teriflunomide. The most common adverse events in the 2 treatment groups were, respectively, nasopharyngitis (45.7%, 50.0%), hypoesthesia (45.7%, 47%), fatigue (40.7%, 47%), headache (45.7%, 33.3%), extremity pain (43.2%, 30.3%), and upper respiratory tract infection (33.3%, 40.9%). Adverse events leading to discontinuation occurred in 21% of those in the 7-mg group and in 18.2% in the 14-mg group. Asymptomatic liver and pancreatic enzyme elevations also occurred in some patients.

Phase 3 safety data for BG-12 (dimethyl fumarate) were released from the DEFINE study,[14] a randomized, double blind, placebo-controlled, multicenter trial. The trial included 1234 patients who received placebo (n = 408), BG-12 240 mg twice a day (n = 410), or BG-12 240 mg 3 times a day (n = 416). The most frequent adverse events were flushing, MS relapse, nasopharyngitis, headache, diarrhea, and fatigue. Flushing was much more common in the BG-12 arms (twice-daily dose, 38%; 3 times-daily dose, 32%) than in the placebo group (5%). No opportunistic infections occurred. Similar numbers of patients in each group withdrew because of adverse events (twice-daily dose, 16%; 3 times-daily dose, 16%; placebo, 13%.)

Safety and efficacy data on fingolimod were presented.[15] Results from 140 of 281 (49.8%) patients who completed 5 years of follow-up with fingolimod (phase 2 plus extension) showed infrequent serious infections (2.1%) and an overall annualized relapse rate of 0.2. Patients who took fingolimod from the beginning of the study were more likely to be relapse free (61% on 1.25 mg and 68% on 5 mg) than those who started on placebo and switched to fingolimod (51%). Dropouts were mostly the result of adverse events (19.9%) and withdrawal of consent (14.6%).

Five-year data were available from the STRATA study,[16] which included 3013 patient-years of natalizumab exposure from patients who completed feeder studies (AFFIRM, SENTINEL, GLANCE) and their open-label extensions. PML developed in a total of 7 patients. These patients had received 33-51 natalizumab doses; 3 of the 7 (43%) had prior immunosuppressant use; and all were anti-JC virus antibody positive. Other serious adverse events included infections and infestations (3%), gastrointestinal disorders (2%), and neoplasms (2%).

Expert Commentary by Howard Zwibel, MD

The field of MS is currently entering an exciting time, with continued updates on long-term safety and efficacy data of commercially available therapies and the advent of new and emerging therapies. It is of the utmost importance for those of us who care for patients with MS to be constantly aware of the most current peer-reviewed data. At ECTRIMS 2011, information was presented that all healthcare providers should find helpful when making clinical decisions for patients who are not doing well on existing therapy. This includes information on the possibility of newer therapies entering the market, additional guidance on potential risks of current therapy and thoughts about how to deal with these risks, as well as new data on symptom management. Symptom management remains a key component of caring for our patients with MS in a comprehensive manner and helping to improve their quality of life. Included in this section are studies that address walking ability, osteoporosis, and tremor. Sequencing therapies is crucial to treating our patients and needs to be considered much earlier than we have done in the past to obtain optimal results in disease control. We need to be vigilant of long-term safety data from the new generation of

disease-modifying therapies and must remain current on strategies to best control possible adverse events that may come with these therapies. Therapeutic advances in the field of MS are becoming quite rapid and present both a magical and complicated time for patients and clinicians alike.

Risk for PML in patients taking natalizumab is lowest in those patients who did not have prior immunosuppressant use, were anti-JC virus antibody negative, and what third factor?

- ◯ Were treated with natalizumab for 1-24 months
- ◯ Were treated with natalizumab for 24-48 months
- ◯ Had EDSS scores between 1 and 4
- ◯ Had EDSS scores > 4

The impact of pregnancy on MS can result in a doubling of the annualized relapse rate during what time period?

- ◯ In the first trimester
- ◯ In the second trimester
- ◯ In the third trimester
- ◯ In first trimester postpartum

Clinical Aspects of MS

Mortality and MS

In a study of all-cause mortality,[17] data spanning 21 years from 372 patients randomly assigned to interferon beta-1b 50 µg (n = 125), interferon beta-1b 250 µg (n = 124), or placebo (n = 123) revealed a 46.8% reduction in all-cause mortality for the treated group compared with the placebo group. The data set had near complete patient ascertainment (98.4%).

Natalizumab

Natalizumab, the first monoclonal antibody therapy against MS, has been prescribed to 83,300 patients for a total of 148,800 patient-years of exposure. As of March 2011, PML had developed in 124 patients, with a survival rate of 81%. Of the first 79 cases in which more detailed data are available, the 63 (80%) survivors tended to be younger (median 43 vs 52.5 years) and had a shorter time to PML diagnosis (34 vs 54 days) compared with those who died. On MRI, PML was widespread in 63% of fatal cases. All of the 38 patients who survived and were followed for at least 6 months after diagnosis had at least some disability: 13% had mild disability, 50% had moderate disability, and 37% had severe disability.[18]

Risk factors for PML in patients taking natalizumab were quantified using data from 5896 general patients with MS and 25 patients with MS and PML who were treated with natalizumab.[19] The risk for PML was greatest in those who received natalizumab for 25-48 months, who had prior immunosuppressant use, and who were anti-JC virus antibody positive (7.8/1000). The risk was lowest in those who were treated with natalizumab for 1-24 months, who did not have prior immunosuppressant use, and who were anti-JC virus antibody negative (< 0.11/1000).

The effect of natalizumab withdrawal was evaluated in the TYSEDMUS cohort, which includes all patients treated with natalizumab in France.[20] Of 2921 patients, 577 (19.75%) stopped natalizumab and were followed for at least 12 months. Women were nearly twice as likely to discontinue natalizumab as men. The most common reasons for discontinuation were "other" (n = 246), lack of tolerance (n = 164), and lack of efficacy (n = 134). Of those who discontinued, 23% (133/577) had at least 1 relapse within 12 months of discontinuation of natalizumab, and 33% had gadolinium enhancement. Most of the relapses occurred between 3 and 5 months. A total of 23% of those who stopped natalizumab started alternate therapy, either immunosuppressive (n = 121) or immunomodulatory (n = 14) therapy. Of those who restarted therapy, more than half (59%) resumed natalizumab.

Mood and Pseudobulbar Symptoms

A 24-month prospective, single-arm, multicenter study that used multiple measures of emotional domains did not detect any significant effect of interferon on mood.[21] The study included 79 patients who were evaluated for emotional dyscontrol, blunted affect, irritability (State-Trait Anger eXpression Inventory, STAXI), fatigue (UK Neurological Disability Scale, UKNDS), depression (Center for Epidemiological Studies Depression scale, CES-D), and anxiety (State-Trait Anxiety Inventory, STAI).

After 2 years of prospective follow-up, the only significant change was in fatigue, which had a transitory increase during the first 6 months of treatment. Interferon beta had no demonstrated effect on mood.

The safety of a new FDA-approved treatment for pseudobulbar symptoms, dextromethorphan/quinidine, was evaluated in 129 patients with MS as part of a study that included 197 patients with amyotrophic lateral sclerosis.[22] The most common adverse events in those with MS were dizziness, nausea, headache, diarrhea, nasopharyngitis, somnolence, falls, fatigue, muscle spasm, and constipation. Seven patients with MS discontinued the study because of adverse events.

Risk Factors for Progression

It is generally accepted that the development of MS depends on a genetic predisposition coupled with 1 or more environmental factors that trigger the disease.

Smoking was explored in several studies. In a large, multinational, retrospective study of 2125 people with MS and 4455 controls, researchers looked at the interaction between smoking and history of infectious mononucleosis and found a pooled OR of 2.0 for infectious mononucleosis and 1.8 OR for smoking. The effect of infectious mononucleosis was significantly higher among nonsmokers, however (OR 2.4), suggesting the risk for MS related to infectious mononucleosis is not increased in the presence of smoking.[23]

Cigarette smoking for more than 19 pack-years was associated with shorter time to progression ($P = .015$), number of first 2-year relapses ($P < .001$), and motor symptoms at MS onset ($P = .029$). Disability developed more rapidly in those with MS who smoked than in those who had never smoked. Those with MS who smoked reached EDSS 6 approximately 5 years earlier than those who did not smoke ($P < .001$).[24] A study in Sweden of 695 patients with MS who had never smoked compared with 1635 controls explored whether being exposed to passive smoking increased the risk for MS. Researchers demonstrated that passive smoking resulted in a mildly increased risk for MS ($P = .003$; OR 1.3).[25]

The 5-year EPIC study examined whether 25-hydroxyvitamin D3 level is associated with the development of new T2 lesions or contrast-enhancing lesions on brain MRI.[26] Measuring annually, researchers found that each 10-ng/mL increase in 25-hydroxyvitamin D3 level was associated with a 15% lower risk for a new T2 lesion developing ($P = .004$) and a 32% lower risk for a gadolinium-enhancing lesion ($P = .002$) developing. Having fewer clinical relapses was also associated with higher vitamin D levels, but those results were not statistically significant.

The impact of pregnancy on the disease course of MS was investigated by researchers who evaluated the effect of pregnancy on annualized relapse rate in 893 pregnancies in 674 women, of whom 87.4% had relapsing-remitting MS.[27] Annualized relapse rate at baseline was 0.32, and this rate decreased during pregnancy to 0.25 in the first trimester, 0.22 in the second trimester, and 0.13 in the third trimester. Annualized relapse rate nearly doubled in the first trimester postpartum, however (0.61; $P < .001$). The annualized relapse rate returned to baseline at 2 years postpartum (0.33).

Expert Commentary by Stephen Krieger, MD

Although many risk factors for progression in MS are not modifiable, including sex, age, and lesion burden at onset, data continue to suggest that several lifestyle choices may influence disease course. Smoking was shown to increase the risk for relapse and disability progression in one study, and even passive smoking conferred a small increased risk for MS incidence in a separate study.[25] These data suggest a role for smoking avoidance or cessation in the comprehensive management of MS. Low vitamin D levels were shown to correlate with the development of new MS lesions in the EPIC trial,[26] providing further evidence that vitamin D supplementation may be protective in MS, a hypothesis that is being tested by the authors in an ongoing prospective study. Both the protective effect of pregnancy and the heightened risk for relapse during the postpartum period were again demonstrated,[27] providing information that may guide the decision to expedite the re-institution of disease-modifying therapies after delivery.

With regard to symptom management and the safety of disease-modifying therapies, interferons were not shown to have a significant impact on depression, anxiety, or emotional dyscontrol in a prospective study of 79 patients.[21] In another study, dextromethorphan/quinidine, a recently FDA-approved treatment for pseudobulbar affect, appears safe and well-tolerated in both patients with MS and amyotrophic lateral sclerosis .[22]

Updated PML outcomes associated with natalizumab treatment were presented.[18] Whereas fewer than 20% of cases of PML were fatal, more than 80% of those with PML were left with moderate or severe disability. The risk for PML was lowest in patients who

were not previously exposed to immunosuppressants and were treated with natalizumab for less than 24 months. To date, no cases of PML have occurred in patients who are anti-JC virus antibody negative. As a counterpoint, several studies demonstrated the re-emergence of MS disease activity after the cessation of natalizumab, highlighting the complex risk-benefit calculation that must be considered for each patient.[11,20]

In contrast, it is refreshing to consider the decreased risk for death seen in the 21-year follow-up study of interferon beta-1b.[17] This study provides evidence of the long-term safety of interferon beta therapy and its potential favorable impact on mortality.

In sum, these data suggest ways to optimize both treatment and lifestyle decisions to maximize long-term clinical outcomes in patients with MS.

Molecular and cellular alterations in grey matter, such as activation of inflammasomes in astrocytes, downregulate metabolic genes important for:

- ◯ Maintaining myelination
- ◯ Axonal regeneration
- ◯ Increased expression of lymphocyte activation pathways
- ◯ Neuronal homeostasis

What inflammatory cell infiltrate in the meninges represents a source of pro-inflammatory cytokines, lytic enzymes, and immunoglobulin that may contribute to the severity of subpial grey matter pathology and an accelerated clinical course of patients with secondary-progressive MS?

- ◯ Ectopic B-cell follicle-like structures
- ◯ Chondroitin sulfate
- ◯ Oligodendrocyte precursor cells
- ◯ Complement factor H

Biomarkers and Neuropathology

RNA profiles of cells extracted from peripheral blood may contain information that discriminates subsets of patients with MS, and this may illuminate the structure within the MS population.[28] Researchers attempted to uncover this structure without assumption about which transcriptional pathways might be important and to relate the subsets to evidence of disease activity. Unsupervised clustering (non-negative matrix factorization) of RNA from frozen peripheral blood mononuclear cells identified 2 subpopulations in each of 3 populations of patients with MS: untreated patients (n = 141), patients treated with glatiramer acetate (n = 94), and patients treated with interferon beta (n = 128). Further, one of the untreated patient subsets was defined by higher expression of lymphocyte activation pathways (such as PI3K/MAP kinase signaling in T and B cells) and was more likely to experience a radiographic or clinical relapse when treated with either glatiramer acetate or interferon beta (P = .0077).

In situ hybridization of 13 brainstem plaques from 3 patients with MS revealed a high signal of complement factor H mRNA, a major regulator of complement activation, in inactive lesions.[29] However, there was an undetectable signal in active lesions. Loss of complement factor H signal in active lesions may indicate lack of production or consumption.

Grey matter pathology in MS may be associated with cognitive dysfunction, fatigue, and seizures. To better understand how the molecular and cellular alterations in grey matter affect clinical deficits, researchers determined that activation of inflammasomes in astrocytes downregulates metabolic genes important for sustaining neuronal homeostasis. They believe that this may contribute to grey matter pathology in MS.[30]

Several experiments by Nakahara and colleagues[31] suggest that the classic demyelinating lesions of MS may be at least partially corrected by resident oligodendrocyte precursor cells (OPCs). A monoclonal antibody targeting clone ex5A1, the extracytoplasmic domain of FcRgamma (gamma chain of immunoglobulin Fc receptor), induced morphologic and biochemical differentiation of mouse OPCs within 24 hours. The same antibody administered intraperitoneally in mice with myelin-oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) resulted in clinical recovery.

A single shot of the antibody stereotactically injected near demyelinated corpus callosum induced remyelination in these chemically demyelinated mice. Further research will determine whether this antibody is a candidate for development as a treatment for MS.

Chondroitin sulfate proteoglycans accumulate after central nervous system injuries and may impede axonal regeneration.[32] In human brain samples from patients with intractable epilepsy, chondroitin sulfate proteoglycans were poor adhesive substrates for OPCs and also impeded maturing oligodendrocytes from elaborating processes, which are necessary for myelination. Protease ADAMTS4, which degrades the core protein of chondroitin sulfate proteoglycans, overcame the inhibitory effect of chondroitin sulfate proteoglycans on adhesion. Protease ADAMTS-4 and chondroitinase ABC, which removes glycosaminoglycan side chains, prevented chondroitin sulfate proteoglycan inhibition of oligodendrocyte process growth. These and other experiments suggest that chondroitin sulfate proteoglycans may be impediments to oligodendrocyte biology and may be potential inhibitors to remyelination.

Ectopic B-cell follicle-like structures were found in 49 of 123 (40%) of patients with secondary-progressive MS and were associated with an increase in diffuse meningeal inflammation, microglial activation, and grey matter cortical demyelination.[33] The degree of meningeal and perivascular inflammation was inversely proportional to the age at conversion to secondary progression of MS, age at necessary wheelchair use, and age at death. Because inflammatory cell infiltrates in the meninges represent a source of pro-inflammatory cytokines, lytic enzymes, and immunoglobulins, they may contribute to the severity of subpial grey matter pathology and an accelerated clinical course in patients with secondary-progressive MS.

In several transgenic mouse models, MOG-induced EAE did not develop in B-cell-deficient mice, indicating that B cells may play a role in the pathogenesis of human MS. Mice with mixed bone marrow chimera that contained major histocompatibility complex (MHC) II+ B cells were susceptible to MOG-induced EAE, but mice containing MHC II– B cells were not. Resistance to EAE was associated with a decrease in peripheral and infiltrating effector inflammatory Th cells. Chimeras that contained MOG-specific MHC II– B cells were resistant to EAE, suggesting that B-cell antigen presenting function, but not transfer of B-cell receptor-captured antigen is important for the development of central nervous system autoimmunity.[34]

MRI

Advances in technology allow improved explorations of the relationship between white matter and deep grey matter lesions in MS. A 3T MRI study of 37 patients with MS (3 patients with clinically isolated syndrome, 30 patients with relapsing-remitting MS, and 4 patients with secondary-progressive MS) and 17 controls demonstrated that the association between white matter tract damage and deep grey matter atrophy was higher in multiple regions in those with MS than in controls.[35] Higher association was shown in the left thalamus and cerebral peduncle ($P = .01$), the right thalamus and posterior corona radiata ($P = .02$), the external capsule ($P = .04$), the cingulum ($P = .01$), the superior longitudinal fasciculus ($P = .01$), and the caudate and external capsule ($P = .01$).

The mean cross-sectional area of the upper cervical spinal cord decreased at 12 and 24 months in 363 patients with MS (264 patients with relapsing-remitting MS, 73 with secondary-progressive MS, 26 with primary-progressive MS) ($P \leq .017$).[36] The cross-sectional upper cervical cord area correlated negatively with EDSS scores ($P < .001$), indicating that neuroimaging of the spinal cord may prove a useful surrogate for disability.

Expert Commentary by Robert Lisak, MD

Recent research has reinforced the view that MS is a complex disorder and that we still have much to learn about the pathogenesis of different phases of the disease. It is unlikely that a single immunopathogenic mechanism will prove to be responsible for the development of individual lesions in the white matter or gray matter in patients with relapsing-remitting MS or for the progressive phases of the disease. Studies of the genetics of MS have shown the complexities of the role of genes in the pathogenesis of MS, and while reinforcing the importance of small changes in sequences (single nucleotide polymorphisms) in DNA, these studies have also made clear that environmental factors, including epigenetic factors, are important in the pathogenesis of MS and likely in the disease's response to the available disease-modifying therapies.

There is a great need for biomarkers of disease activity and for biomarkers that predict, as early as possible, patient responses to disease-modifying therapies. A study reported at ECTRIMS provided evidence that not treating patients and nonresponse to therapy are associated with activation of RNA specific for pro-inflammatory activation molecules in inflammatory cells.[28] This would be a step toward providing a marker. It is unlikely that a single gene, transcript, or protein will fulfill all needs.

The role of regulatory proteins and other factors in the complement cascade continue to be of interest. Antibodies have a potential role in the pathogenesis of MS, and some complement-related molecules have chemoattractant effects.

The increased recognition early in the course of MS of gray matter pathology and its importance have resulted in more studies attempting to understand how myelin and neurons/axons within gray matter are damaged. In MS as in many neurodegenerative disorders and processes, the cell that seems to bear the brunt of the damage may not be the only cell involved in the disease process. The role of astrocytes in mediating gray matter damage or failing to protect oligodendrocytes and neurons is of increasing importance. Astrocytes are clearly important in the development and maintenance of synapses.

Newer MRI techniques are increasingly being used to aid in the understanding of the relationship between white matter and gray matter involvement. Improved technology has also made it possible to study and quantify changes in the spinal cord. These seem to correlate with disability in patients with relapsing-remitting MS and in those with progressive forms of MS. The increased use of quantitative spinal cord imaging in clinical studies and eventually in clinical practice is likely.

The role of B cells in the pathogenesis of MS has also attracted increased interest because they may damage both white and gray matter. Traditionally, B cells have been of interest as cells that mature to become immunoglobulin-secreting plasmablasts and plasma cells, but recent research, including studies on the effects of agents directed against B cells, has brought attention to other roles of B cells in MS. The finding of B cells in follicle-like structures in the meninges of patients with secondary-progressive MS has been reported before, but more recent studies emphasize their association with gray matter pathology and now with markers of disease severity.[33] In an animal model of MS, EAE, B cells could present antigen to CD4 T cells in the context of MHC class II molecules were associated with induction of EAE, but B cells that did not express MHC class II antigens did not induce disease. However, MHC class II B cells in chimeras that had specific sensitizing antigen for this model of EAE inhibited disease, emphasizing the downregulatory functions of B cells in the disease process in certain circumstances.[34]

Neuroprotection and repair and restorative processes are also of increasing importance in MS. Proteoglycans appear to inhibit myelin repair in several models, including trauma, and also inhibit axonal outgrowth.[32] Strategies to inhibit chondroitin sulfate proteoglycans and other molecules that limit myelin and neuronal repair will be of increasing interest, as will stimulation of oligodendrocyte precursors, which seem to be spared in lesions in early relapsing-remitting MS.

Summary

There are currently a wide variety of oral and injectable treatments for MS that offer improved efficacy but sometimes at the risk for novel and potentially serious complications. New and improved treatment options are good news for patients but greatly increase the complexity of therapeutic decision-making for the practicing neurologist. The 21-year follow-up study of interferon beta-1b demonstrated a reduction in all-cause mortality, further raising the stakes of a decision to forego treatment because of concern for adverse effects.[18]

Avoiding serious complications such as PML is imperative. As risk factors such as prior immunosuppressive therapy, duration of natalizumab treatment, and anti-JC virus antibody status are confirmed, treatment strategies that include risk-factor modification and switching to other therapies are evolving. Risk-factor modification for disease progression should also be directed toward environmental factors such as cigarette smoking. Prospective studies such as SUMMIT, which enrolled 1500 patients, will likely highlight additional risk factors for disease progression. MRI continues to be important in following disease activity and progression, and MRI of the upper cervical cord may be important to include as well.

Symptomatic treatments such as dalfampridine to improve walking speed, dextromethorphan/quinidine for pseudobulbar affect, and onabotulinum A toxin for tremor have also joined the therapeutic armamentarium. Research continues into the multifaceted pathophysiology of MS, and MRI modeling promises to reveal the relationship between white and grey matter lesions. These and other advances lead the way toward more effective and safer therapies for patients with MS.

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