SUPPLEMENT TO
NEUROLOGY REVIEWS
JANUARY 2016

2015 MS HIGHLIGHTS: The Year in Review

Researchers Investigate New Myelin-Repair Strategies

Exogenous methods are in preclinical trials, and some endogenous strategies are now in human studies.

BARCELONA—Researchers are actively seeking means of promoting myelin repair in patients with multiple sclerosis (MS), and some drugs have advanced from the preclinical to the clinical phase, according to an overview presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). The therapy furthest along in development is the anti-LINGO1 monoclonal antibody, which promotes endogenous remyelination. Exogenous strategies for myelin repair are still in preclinical stages, and perhaps the most promising of these methods relies on induced pluripotent stem cells.

"There is still a crucial need of markers: clinical markers of repair, biomarkers of repair, [and] imaging markers of repair," said Catherine Lubetzki, MD, PhD, Professor of Neurology at Pierre and Marie Curie University in Paris. Trial designs for remyelinating strategies also need to be optimized, she added.

Exogenous Strategies

Exogenous strategies introduce myelinating cells into the patient. Oligodendrocyte progenitor cells (OPCs), Schwann cells, and neuronal stem cells are under investigation as potential exogenous methods of remyelination.

Induced pluripotent stem cells have been the major advance in this area in the past several years, said Dr. Lubetzki. Investigators use a mixture of transcription factors to induce skin fibroblasts to become stem cells, and then reprogram them into an oligodendrocyte cell phase. This method can enable autologous grafts. Goldman and colleagues transplanted OPCs generated from human fibroblasts into the brains of dysmyelinating mutant mice. The OPCs promoted extensive remyelination and improved the mice's survival.

Selecting Candidates Based on Their Mechanisms

One method of selecting drug candidates that could promote endogenous remyelination is based on the molecules' mechanisms of action. Dr. Lubetzki and colleagues studied eliprodil because of its known neuroprotective properties. In 1999, they demonstrated that eliprodil strongly stimulated CNS myelination in an in vitro system of myelination.

More recently, Dr. Lubetzki and colleagues have been investigating molecules that guide OPCs to demyelinated areas. In a proof-of-concept study, the investigators found that semaphorin 3F performs such a function. They also concluded that speeding the recruitment of OPCs to demyelinated plaques results in accelerated remyelination. Approximately one year ago, the team began an ongoing preclinical study in which they are overexpressing semaphorin 3F at lesion sites to speed the recruitment of OPCs and accelerate the remyelination process. The goal is to stimulate remyelination during the window of time when axonal damage is reversible, said Dr. Lubetzki.

Perhaps the best-known investigational strategy for promoting endogenous repair involves the protein LINGO1. Researchers at Biogen found that when LINGO1 is expressed at the surface of immature oligodendrocytes, the protein blocks their maturation and prevents myelination. They developed a monoclonal antibody to suppress the expres-

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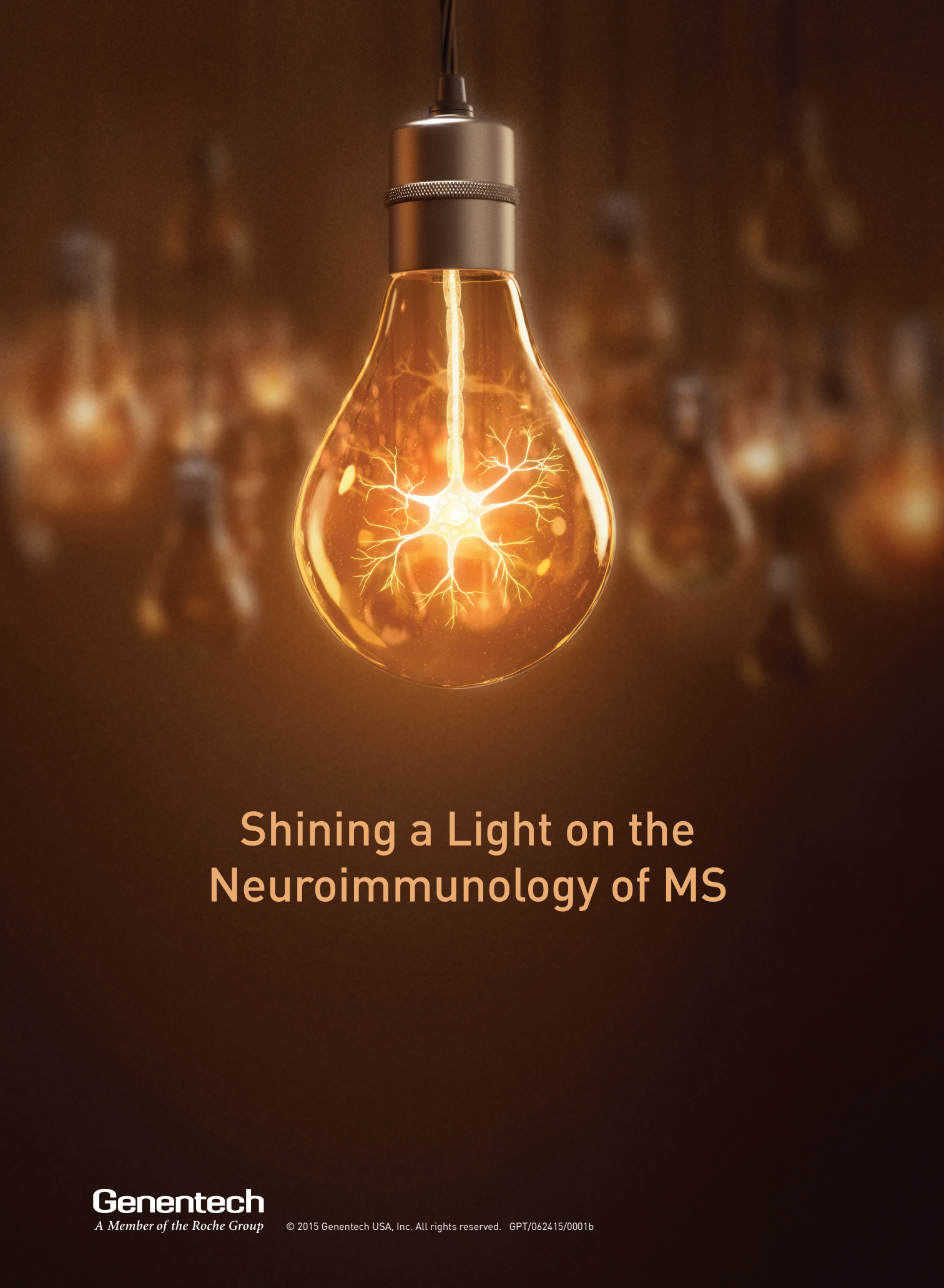

Shining a Light on the Neuroimmunology of MS

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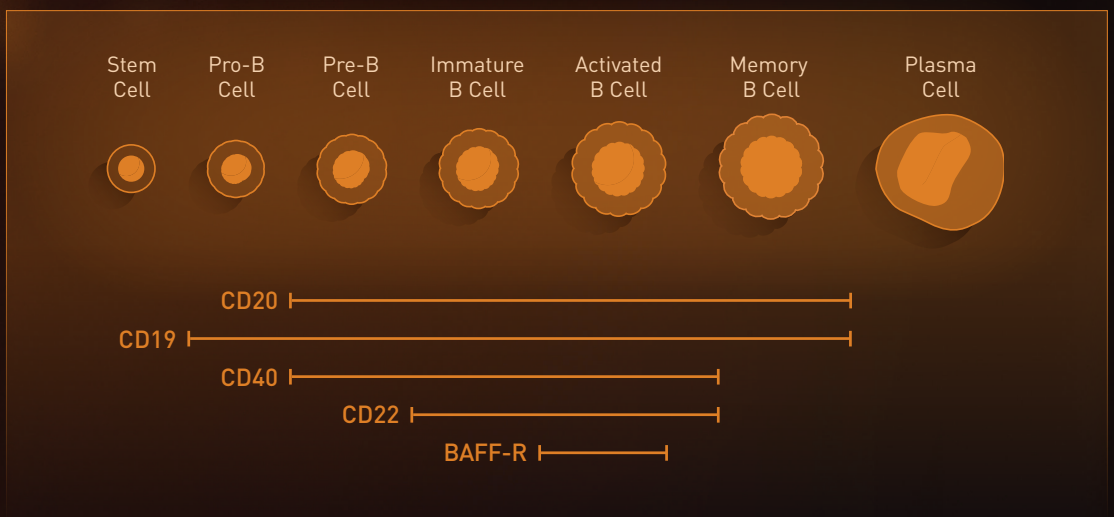
B cells, like T cells, are diverse and play multiple roles in the inflammatory cascade of MS[1-3]

Mature B cells can activate T cells in the CNS through antigen presentation, and can release proinflammatory cytokines.[2-6] Plasma cells produce antibodies, which recruit other immune cells to destroy tissue.[2,5]

B cells express different cell surface markers as they mature[2,7]



Adapted from Blüml S *et al. Arthritis Res Ther.* 2013;15(suppl 1):S4-S25, under Creative Commons License CC BY 2.0.

LEARN MORE ABOUT B AND T CELLS AND MS PATHOGENESIS AT MSIMMUNOLOGY.COM

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Researchers Investigate New Myelin-Repair Strategies

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sion of LINGO1, thus allowing oligodendrocytes' maturation to proceed and improving myelination and remyelination.

The anti-LINGO1 monoclonal antibody yielded positive results in experimental models, and investigators subsequently began two phase II studies of the treatment in humans. Results of the first study were reported at ECTRIMS; the monoclonal antibody improved full-field visual evoked potential latency in patients with acute optic neuritis, and this result was consistent with improved remyelination. The other phase II study includes 419 patients with relapsing-remitting MS and is ongoing.

Screening Banks of Molecules

The other main approach to selecting drug candidates that could promote endogenous remyelination is to screen a large bank of molecules. This approach "will lead to an increasing number of candidates and new screening tools," said Dr. Lubetzki.

Several years ago, Tesar and colleagues developed a method of deriving OPCs from epiblast stem cells. The investigators recently used this cellular model to perform high-throughput screening of a large library of bioactive small molecules. They identified seven compounds that, at low concentrations, enhanced the generation of mature oligodendrocytes from OPCs. After they validated this method in various models, Tesar and colleagues identified two drug candidates: miconazole, an antifungal drug, and clobetasol, an immunosuppressant. The researchers now have "a strong rationale for translation into human subjects with MS," said Dr. Lubetzki.

In 2014, Chan et al developed a micropillar array system for screening molecules. Oligodendrocytes placed in the array are able to wrap membrane around the micropillars, and investigators can measure the thickness of the membrane. The method thus is a binary indicant of the presence or absence of myelination. When Chan and colleagues used the micropillar array model to perform high-throughput screening, they identified a cluster of antimuscarinic compounds that enhanced oligodendrocyte differentiation. One of these drugs was clemastine, an antihistaminic compound that promotes myelination. Researchers are studying clemastine as a remyelinating agent in an ongoing phase II study of 50 patients with relapsing-remitting MS.

Finally, Zalc and colleagues developed a method of medium-throughput screening based on a transgenic tadpole model. Adding metronidazole to the water bath in which the tadpole swims causes a drastic reduction in the number of oligodendrocytes within the tadpole's optic nerve. When researchers remove the metronidazole from the bath, new oligodendrocytes form within the optic nerve. Zalc and colleagues have used the model to analyze drugs that appear to promote remyelination, such as clemastine, benztropine, and retinoic acid.

One question that researchers have not resolved yet is whether newly formed myelin, which is thinner than normal myelin, is as durable as myelin formed in the normal way. "Twenty years after remyelination, will this myelin be as resistant as the normally made myelin? We don't know. But at least for the short term or the medium term, this newly formed myelin seems to be as efficient as the usually formed myelin," concluded Dr. Lubetzki. **NR**

—Erik Greb

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Ocrelizumab May Reduce Disability Progression in People With Primary Progressive MS

Study findings validate the hypothesis that targeting B cells is a viable strategy for treating progressive MS.

BARCELONA—In people with primary progressive multiple sclerosis (MS), treatment with ocrelizumab may significantly reduce the progression of clinical disability sustained for at least 12 weeks, compared with placebo, according to results from a pivotal phase III study presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). In the study, which is called ORATORIO, clinical disability was measured by the Expanded Disability Status Scale (EDSS).

Ocrelizumab is an investigational, humanized monoclonal antibody designed to selectively target CD20-positive B cells. CD20-positive B cells are a type of immune cell thought to be a key contributor to myelin damage and axonal damage. Preclinical studies suggest that ocrelizumab binds to CD20 cell-surface proteins expressed on certain B cells, but not on stem cells or plasma cells, thus potentially preserving important functions of the immune system.

Ocrelizumab is the first investigational medicine to show a clinically meaningful and statistically significant effect on the progression of disease in primary progressive MS.

The ORATORIO trial was a randomized, double-blind, global multicenter study. Researchers administered placebo or 600 mg of ocrelizumab by IV infusion every six months to 732 people with primary progressive MS. The doses of ocrelizumab were given as two 300-mg infusions two weeks apart. The primary end point of the study was time to onset of confirmed disability progression, defined as an increase in EDSS that is sustained for at least 12 weeks.

Overall, the incidence of adverse events associated with ocrelizumab was similar to that of placebo. The most common adverse events were mild-to-moderate infusion-related reactions. The incidence of serious adverse events associated with ocrelizumab, including serious infections, was also similar to that of placebo.

"People with the primary progressive form of MS typically experience symptoms that continuously worsen after the onset of their disease, and there are no approved treatments for this debilitating condition," said Sandra Horning, MD, Chief Medical Officer and Head of Global Product Development for Genentech, the developer of the therapy. "Ocrelizumab is the first investigational medicine to show a clinically meaningful and statistically significant effect on the progression of disease in primary progressive MS."

In addition to ORATORIO, the phase III clinical development program for ocrelizumab includes OPERA I and OPERA II, which are randomized, double-blind, double-dummy, global multicenter studies in people with relapsing forms of MS. The results of the studies appear to validate the hypothesis that B cells are central to the underlying biology of MS. Genentech plans to pursue marketing authorization for ocrelizumab in relapsing MS and in primary progressive MS. The company will submit data from the OPERA I and II studies and from the ORATORIO study to the FDA in early 2016. **NR**

Anti-JCV Antibody Index and L-Selectin Hone PML Risk Stratification During Natalizumab Therapy

Adherence to a risk-stratification algorithm could prevent as much as 85% of cases of PML.

BARCELONA—The anti-JCV antibody index and L-selectin (CD62L) have merit for risk stratification and share a potential biological relationship with implications for general progressive multifocal leukoencephalopathy (PML) etiology, according to research presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). "A risk algorithm incorporating both biomarkers could strongly reduce PML incidence," said Nicholas Schwab, PhD, of the Department of Neurology at the University of Münster in Germany.

Natalizumab treatment is associated with PML development, with more than 541 cases as of March 3, 2015. Treatment duration, prior immunosuppressant use, and JCV serostatus are currently used for categorical risk stratification, but PML incidence continues to rise steadily. Anti-JCV antibody index and L-selectin (CD62L) have previously been proposed as additional risk-stratification parameters. Dr. Schwab and his research colleagues aimed at verifying and integrating both parameters into one applicable algorithm for risk stratification.

"The combined use of JCV serology and CD62L level found 2% of patients studied to be at highest risk," Dr. Schwab reported. "Adherence to the risk-stratification algorithm might prevent up to or over 85% of PML cases."

The research team gathered international cohorts of patients with multiple sclerosis who were treated with natalizumab. The participants were assessed for JCV index (1,921 control patients and nine pre-PML patients) and CD62L (1,257 control patients and 17 pre-PML patients).

Low CD62L in natalizumab-treated patients was retrospectively confirmed and prospectively validated as a biomarker for PML risk. The risk factor "CD62L low" increased a patient's relative risk 55-fold. Validation efforts established an 86% sensitivity and 91% specificity for CD62L and 100% sensitivity and 59% specificity for JCV index as predictors of PML.

Low CD62L values were also found in various other PML associations and stages (ie, lupus, lymphopenia, HIV, acute natalizumab-PML). CD62L values correlated with JCV serostatus, so the lower the CD62L value of a patient was, the higher the probability that they were JCV positive. The researchers ultimately found that 26 out of 27 (96%) patients with low CD62L were JCV positive. Additionally, CD62L values negatively correlated with JCV index values.

"The combined use of JCV serology and CD62L level found 2% of patients studied to be at highest risk," Dr. Schwab reported. "Adherence to the risk-stratification algorithm might prevent up to or over 85% of PML cases," he said. **NR**

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The Gut Microbiome May Aid the Treatment and Prevention of MS

Future research could examine how the gut microbiota changes over time in patients with MS.

INDIANAPOLIS—The community of organisms housed in the intestines—the gut microbiome—may differ significantly between patients with multiple sclerosis (MS) and healthy controls, preliminary study results show.

"The most exciting possibility is that the gut holds the key to the cause of MS, especially since it has been theorized that MS may be caused by a virus or bacterium," said Howard L. Weiner, MD, at the 2015 CMSC Annual Meeting. "It is also possible that the microbiome, diet, oral tolerance, and antibiotic use relates to MS susceptibility. Modulating the microbiome with probiotics or specific bacteria may be a way to treat MS." These findings could help pave the way toward developing a vaccine to prevent the disease from occurring, Dr. Weiner added.

Modulating the Immune Response

Microbiota in the human body reside in various areas, including the oral cavity, the vagina, and the skin. As many as 500 trillion bacteria and other organisms live in the 300 m^2 of the intestinal tract, explained Dr. Weiner, Robert L. Kroc Professor of Neurology at Harvard Medical School in Boston; founder of the Partners MS Center in Brookline, Massachusetts; and Codirector of the Center for Neurologic Diseases at the Brigham and Women's Hospital in Boston.

"There are more genes in our gut than in any other part of our body," he said. "The gut is probably the largest lymphoid organ in the body and it is where you can induce all kinds of immune responses."

In a relapsing-remitting mouse model of spontaneously developing experimental autoimmune encephalomyelitis (EAE), animals raised in a normal environment became sick, whereas those raised in a germ-free environment did not. The germ-free animals developed EAE, however, after microbial exposure (ie, consuming feces).

"This [result] is clear proof that the gut is important for immune mechanisms in EAE," Dr. Weiner said. Other animal research has shown that colonization with *Bacteroides fragilis* can modulate EAE, he added.

In an ongoing, unpublished study involving an animal model of EAE, Dr. Weiner and colleagues are collecting feces at various stages of disease from onset to recovery. "We then feed the feces to healthy animals. Our preliminary results show that healthy animals fed feces from the peak of disease developed immunity against EAE. It seems that protective organisms develop in the gut as the animals are recovering from disease."

The Human Microbiome

One study showed that the gut of patients with rheumatoid arthritis is enriched with *Prevotella copri*. "However, we don't have a clear handle on the effect of microbiota on human disease because there are so few studies on the subject."

In a recent study, Dr. Weiner and colleagues collected blood and stool samples from 63 patients with MS and 43 healthy controls. Of the patients with MS, 18 were being treated with beta interferon and 14 with glatiramer acetate; 29 were untreated. Exclusion criteria included antibiotic or probiotic use; recent gastroenteritis; a history of irritable bowel disease, rheumatoid arthritis, or systemic lupus erythematosus; recent travel history; history of bowel surgery; and treatment with prednisone, mycophenolate mofetil, mitoxantrone, rituximab, IV immunoglobulin, or methotrexate.

"We extracted the genetic material from the stool samples and sequenced the hypervariable regions of the 16S using three platforms," Dr. Weiner said. "We used a Roche 454 sequencing system, as well as Illumina sequencing, which is deeper, but more restrictive. Then we performed validation with quantitative polymerase chain reaction analysis."

There was no difference in the diversity of bacteria in the gut between patients with MS and controls. However, *Methanobrevibacter smithii* and *Akkermansia muciniphila* were increased and *Butyricimonas virosa* was decreased in patients with MS.

"This is an interesting finding, as *Butyricimonas* produces butyrate, which typically is reduced in MS and other

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autoimmune diseases. Because butyrate induces regulatory cells, this [result] goes along with our theories about MS."

Network analysis indicated that *Methanobrevibacter, Akkermansia,* and *Butyricimonas* were linked to the same gene module in monocytes. "This finding implies that the changes in the gut for these organisms in MS patients are not independent of each other," Dr. Weiner said. "More research is needed to confirm this [finding], but we certainly have found some interesting leads."

Collinsella aerofaciens, Slackia exigua, and *Prevotella* were decreased in untreated patients with MS. Patients receiving glatiramer or interferon therapy had increased *Prevotella, Sarcina lutea,* and *Sutterella wadsworthensis.* "In the future, we plan to test patients who are on other MS drugs, as well."

Spotlight on *Methanobrevibacter*

"We looked closely at *Methanobrevibacter*, which is not a bacterium, but is actually an archaeon," Dr. Weiner noted. "We took 10 patients with *Methanobrevibacter* and 10 patients without it to see if there were any differences in their monocytes and lymphocytes." The researchers found that monocytes and T cells had unique transcription profiles in *Methanobrevibacter*-positive patients.

Antigen array profiles measuring the activity of serum antibodies showed increased reactivity to tetracosonoic acid in *Methanobrevibacter*-positive patients with MS. Patients with high reactivity to *Methanobrevibacter* lysates also had increased expression of a specific gene module within T cells. Reactivity to *Methanobrevibacter* lipids in patients with MS was strongly associated with interferon γ and tumor necrosis factor α pathways in T cells. "This is an important finding because it is believed that interferon γ and tumor necrosis factor α play an important role in MS," said Dr. Weiner.

Keeping in mind that *Methanobrevibacter* is a methane-producing organism, he and his colleagues performed breath tests on a separate group of 30 patients with MS and 30 healthy controls. Breath methane concentrations were elevated in patients with MS, compared with controls. "This [finding] also raises the possibility that breath tests are an easier way to look into the gut than taking stool samples," Dr. Weiner said.

Future Considerations

According to Dr. Weiner, future explorations should include longitudinal studies of stool samples from patients with MS, examininations of how changes in gut bacteria relate to MRI findings and disability, and trials of probiotics. **NR**

—Adriene Marshall

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Drug May Yield Clinical Improvement for Patients With Progressive MS

Data suggest that the vitamin biotin may reduce disability in patients with progressive MS.

WASHINGTON, DC—Biotin may result in clinical improvement among patients with progressive multiple sclerosis (MS) and decrease the risk of progression, according to a study described at the 67th Annual Meeting of the American Academy of Neurology. The drug appears not to be associated with any significant adverse events.

Many MS therapies have reduced relapses effectively but have failed to produce significant and sustained reductions in disability. In an open-label study published in 2015, patients with progressive MS who received high doses of biotin had 22% clinical improvement, mainly in the Expanded Disability Status Scale (EDSS). Ayman Tourbah, MD, PhD, Professor of Neurology at Centre Hospitalier Universitaire in Reims, France, and colleagues subsequently conducted a phase III trial of MD1003, a highly concentrated pharmaceutical grade of biotin, at 16 MS reference centers.

Comparing MD1003 and Placebo

Eligible participants were between ages 18 and 75, had primary or secondary progressive MS, had an EDSS score between 4.5 and 7, and had disease progression within the previous two years, as measured by EDSS. Patients were excluded from the study if they had initiated a new disease-modifying therapy during the three months before enrollment or if they had received symptomatic treatment with fampridine within one month of enrollment.

The researchers screened 166 patients and included 154 of them in a two-to-one randomization. In all, 103 patients received daily 300-mg doses of MD1003, and 51 patients received placebo. Slightly more patients in the active arm had primary progressive MS, compared with the placebo group. Also, slightly more patients were taking fampridine in the placebo group, compared with the active group. The researchers noted no other differences between the treatment arms.

The study's primary end point was the proportion of patients with improvement at month nine that was confirmed at month 12 using EDSS or the Timed 25-Foot Walk (T25FW), compared with baseline measures. EDSS improvement was defined as a decrease of at least one point for patients with a baseline EDSS between 4.5 and 5.5, and as a decrease of at least 0.5 points for patients with a baseline EDSS between 6 and 7. T25FW was considered improved if it decreased by at least 20%, compared with baseline.

Treated Patients Had Sustained Improvement

At the end of the study, 13 patients in the active arm had met the primary end point, compared with none of the patients in the placebo arm. The difference between groups was statistically significant. Twice as many patients met the primary end point with the EDSS, compared with the T25FW. The investigators found no major differences between the group of patients treated with MD1003 and the group of patients who met the primary end point.

A secondary analysis indicated that mean EDSS improved at the initial phase of the trial for participants in the treatment arm, and their improvement was sustained throughout the study. The placebo group had an initial improvement in mean EDSS, but EDSS worsened at all subsequent time points. After 12 months, the difference between the two groups in the mean change in EDSS was statistically significant.

In addition, 13.6% of patients in the placebo group had EDSS progression that was confirmed at two subsequent visits. In contrast, 4.2% of patients receiving MD1003 had progression at month nine that was confirmed at month 12. The difference between groups was not statistically significant, however. Nevertheless, the data indicate a 67% decrease in the risk of progression for patients receiving MD1003, compared with controls, said Dr. Tourbah. Similar trends were observed for the T25FW.

The researchers found no difference in adverse events between the treatment groups. Twice as many patients in the placebo group had relapses, compared with the active arm. High doses of biotin may interfere with immunoas-

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says that use biotinylated antibodies or substrates, however, thus requiring patients and physicians to be informed adequately.

Biotin is a water-soluble coenzyme that is thought to promote myelination and enhance energy supply. "High doses of biotin may feed the Krebs cycle to increase adenosine triphosphate synthesis and energy production, thus possibly reversing virtual hypoxia and protecting neurons from degeneration," said Dr. Tourbah. **NR**

—Erik Greb

Data Provide Additional Evidence of Biotin's Efficacy

The concept that biotin, a water-soluble vitamin, could have a beneficial effect on the course of multiple sclerosis (MS) is biologically plausible. Biotin activates acetyl-CoA carboxylase, a potential rate-limiting enzyme in myelin synthesis, and has multiple other biochemical effects.

In a small consecutive pilot study in 2015 that was neither placebo-controlled, blinded, nor randomized, Sedel et al found a suggestion of high-dose biotin's clinical efficacy in patients with progressive MS.

The follow-up study by Tourbah et al expanded and confirmed the clinical efficacy of high-dose biotin (in the form of MD1003) in progressive forms of MS. In contrast to the prior trial, this trial was a double-blind, placebo-controlled, randomized study of 154 patients treated with 300 mg of biotin or placebo daily for 48 weeks. The results indicated that 13.6% of 103 biotin-treated patients had improvement of disability, using change in Expanded Disability Status Scale score or Timed 25-Foot Walk from baseline, as compared with 51 placebo-treated patients. No serious side effects were reported.

Few, if any, studies have shown sustained clinical improvement in patients with progressive forms of MS to date. As is often the case, however, some patients with ostensibly progressive MS may have evidence of clinical relapses, as seen in the biotin trials, or subclinical MRI relapses, as seen by new T2 or enhancing lesions in other studies, that may respond transiently to corticosteroids or disease-modifying therapies.

The mechanism of action of biotin in progressive MS, if validated in other studies, is not well defined. Possibilities include remyelination, axonal regeneration, inhibition of free oxygen radicals, and other effects. Biotin's efficacy probably is not due to immunosuppression, however.

The results of Dr. Tourbah's study are consistent with previous animal and human data that indicate biotin's excellent safety profile. For this reason, and in light of the lack of treatment efficacy in progressive MS, additional robust phase III studies of biotin should be carried out in an attempt to corroborate and expand these findings. This effort should include a larger number of patients with a longer study duration and additional clinical, neuropsychologic, and MRI studies.

—Stuart D. Cook, MD
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Risk Stratification Can Guide the Choice of MS Treatment

Various strategies can mitigate the risk of adverse events associated with disease-modifying therapies.

BOSTON—The emergence of many new disease-modifying therapies in the past 10 years has made it more challenging to choose a drug for a patient with multiple sclerosis (MS), according to an overview provided at the 2014 Joint ACTRIMS–ECTRIMS Meeting. In the United States, 12 FDA-approved therapies, including oral medications, are available for the long-term treatment of MS. These medications' efficacy, tolerability, and safety differ widely, and patient-specific risk factors can be an important guide for choosing the appropriate treatment, said Robert Fox, MD, Vice Chair for Research at the Cleveland Clinic.

Head-to-head comparisons indicate great similarity among injectable MS therapies, which generally reduce annualized relapse rate by about 30%. The choice of an injectable therapy should be influenced by the expected side effect profile, the patient's risk factors, patient preference about the frequency of administration, and the clinician's comfort with the drug, said Dr. Fox. Risk stratification and mitigation should continue over time because risk factors can change, thus altering an individual's risk for a complication.

Interferon and Glatiramer Acetate

Interferon and glatiramer acetate are considered relatively safe medications, but they still require risk evaluation and mitigation, Dr. Fox said. Nonsteroidal anti-inflammatory agents and hydration can mitigate interferon's flu-like side effects, and monitoring can reduce the drug's associated risks of increased liver enzymes and leukopenia. Screening patients for headache, pain syndromes, and depression is also warranted before and during interferon treatment.

Glatiramer acetate entails risks of erythema, lipoatrophy, induration, and immediate post injection systemic reaction. Education and proper injection technique can mitigate the risk of skin reactions, and "education is of high importance for the post injection systemic reaction and can help avoid needless trips to the emergency room," said Dr. Fox.

Natalizumab

Researchers have identified three main factors that can stratify the risk for progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab: John Cunningham virus (JCV) infection, prior immunosuppressant use, and duration of natalizumab treatment. Patient counseling and decision making depend greatly on which risk factors the patient has, said Dr. Fox.

Natalizumab is considered relatively safe for patients who are JCV negative, but seroconversion may occur over time. Neurologists can consider other therapies for individuals who are JCV positive, but if good alternatives are not available, the clinician may consider limiting natalizumab treatment to one to two years. Natalizumab should be avoided for patients with prior immunosuppressant use if reasonable alternatives are available. Neurologists should be vigilant for symptoms suggestive of PML and could consider performing an MRI at least every six months in JCV seropositive patients.

Antinatalizumab antibodies, which can develop particularly with prior natalizumab use, and history of anaphylaxis increase the risk of allergic reactions to natalizumab, Dr. Fox noted. Liver enzyme screening at baseline and close monitoring for patients with a history of liver disease can mitigate the risk of elevated liver enzymes.

Fingolimod

Fingolimod, particularly the first dose of the drug, entails a risk of cardiac events, and concomitant medications can increase this risk. Obtaining a cardiac history is advisable before patients start fingolimod. In addition, neurologists should perform baseline EKG, first-dose observation, and a post first-dose EKG for the patient. A standard observation lasts for six hours and includes frequent monitoring of vital signs. A 24-hour observation is indicated in patients with certain risk factors.

Fingolimod also carries a risk of macular edema that may be higher in older people or those with a history of diabe-

Risk Stratification Can Guide the Choice of MS Treatment

tes or uveitis. Neurologists therefore should perform optical coherence tomography at baseline and at three months, said Dr. Fox. Patients with visual symptoms should be evaluated promptly for possible macular edema.

Because the drug is associated with a risk of herpes virus infections, patients should be screened for varicella zoster serology, even if they have a history of chicken pox. Seronegative patients require vaccination before starting fingolimod. Other risks include lymphopenia and leukopenia, and neurologists can monitor for these outcomes through intermittent complete blood count testing. Repeated liver function panels may mitigate the risk of increased liver enzymes, and headaches and back pain can be treated symptomatically.

Teriflunomide

Teratogenesis may be the biggest concern for patients treated with teriflunomide, which is labeled as pregnancy category X. Alternative therapies could be considered for people of childbearing potential, said Dr. Fox. Patients who receive teriflunomide should use contraception. Certain treatments can accelerate washout if a patient wants to become pregnant or inadvertently becomes pregnant while taking teriflunomide.

Teriflunomide may increase liver enzymes, therefore monitoring is appropriate. The drug is relatively contraindicated for patients with previous liver injury secondary to medications, liver disease, or tuberculosis, added Dr. Fox.

Dimethyl Fumarate

Flushing occurs in one-third of patients taking dimethyl fumarate. This side effect is benign and typically passes in 20 minutes. Taking aspirin daily can prevent flushing or reduce its severity.

One-third of patients may experience gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain. The symptoms typically improve after one month. Administering the drug with food, titrating the dose slowly, and providing symptomatic treatments may help.

Dimethyl fumarate also is associated with lymphopenia, which typically takes around 12 months to develop. It is reasonable to monitor patients for lymphopenia, particularly at 12 months, and for infections, said Dr. Fox.

The drug also may be associated with a risk of PML. Four cases of PML have been reported from a total experience of approximately 170,000 patient years. Patients with PML had been receiving a formulation of dimethyl fumarate used to treat psoriasis, and some had prior immunosuppressant use and prolonged lymphopenia. After the ECTRIMS meeting, the manufacturer reported a case of PML in a patient with MS receiving dimethyl fumarate who had low lymphocyte counts for 3.5 years. Compared with natalizumab, dimethyl fumarate is associated with a lower risk of PML. "Nonetheless, it's something that we're keeping in the back of our mind and watching for," said Dr. Fox. Monitoring for severely reduced lymphocyte counts may mitigate the risk of PML, he concluded. **NR**

—Erik Greb

Suggested Reading

Baldwin KJ, Hogg JP. Progressive multifocal leukoencephalopathy in patients with multiple sclerosis. *Curr Opin Neurol.* 2013;26(3):318-323.

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Perumal J, Khan O. Emerging disease-modifying therapies in multiple sclerosis. *Curr Treat Options Neurol.* 2012;14(3):256-263.