A SUPPLEMENT TO
NEUROLOGY REVIEWS

MS NEWS From the 2017 AAN & CMSC ANNUAL MEETINGS

How Can We Predict Whose MS Will Worsen?

Two factors predict conversion to secondary progressive MS.

Bianca Weinstock-Guttman, MD

BOSTON—In older people with multiple sclerosis (MS), fatigue and limited lower leg function are more common in people with MS progression than in those without, according to a preliminary study presented at the 69th Annual Meeting of the American Academy of Neurology.

"Study participants with those symptoms were more likely to progress from relapsing-remitting MS to secondary progressive MS within five years," said study author Bianca Weinstock-Guttman, MD, a Professor in the Department of Neurology at the Jacobs School of Medicine and Biomedical Sciences at the University of Buffalo in New York. "Better understanding of who is at high risk of getting worse may eventually allow us to tailor more specific treatments to these people."

Older age at disease onset, high frequency of relapses, and male sex have been found to be predictive of higher risk of conversion to secondary progressive MS. To further define predictors of disease progression, Dr. Weinstock-Guttman and colleagues investigated patient-reported outcomes in an aging cohort of patients with MS.

For the study, 155 people age 50 or older who had had relapsing-remitting MS for at least 15 years were evaluated for symptoms and level of disability at the beginning of the study and five years later, at which point they had been living with MS for an average of 22 years. The study subjects were part of the New York State MS Consortium.

In all, 30.3% of people in the study had progressed to secondary progressive MS by the five-year mark. Those who progressed to secondary progressive MS were older at study enrollment (54.8 vs 52.1) and had a higher Expanded Disability Status Scale score at baseline (3.5 vs 2.6) and at year 5 (5.6 vs 3.0). Those who progressed at year 5 were more likely to report lower limb problems at baseline (53.2% vs 21.5%; odds ratio, 3.0) and were more likely to report fatigue (91.5% vs 68.2%; odds ratio, 4.2), compared with those whose disease did not progress. The results were the same after researchers adjusted for other factors that could affect disease progression, such as age, disease duration, and disability severity.

"While more research needs to be done, this study brings us closer to understanding which older adults with MS may be at higher risk of getting worse," said Dr. Weinstock-Guttman. "With the aging population, this information will be vital as people with MS, their families, and policy makers make decisions about their care." The investigation was supported by the National MS Society. ■

—Glenn S. Williams

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WHAT'S MS'ING?

UNCOVERING THE
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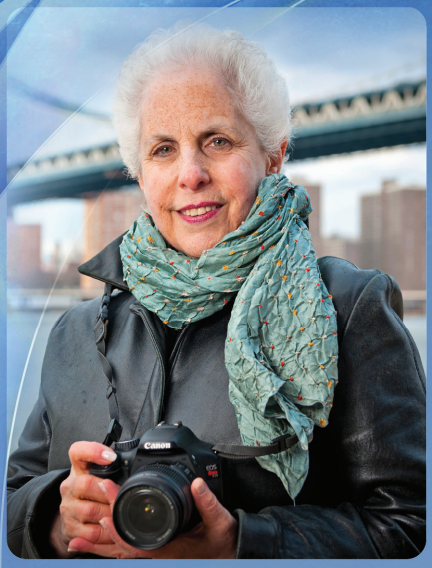
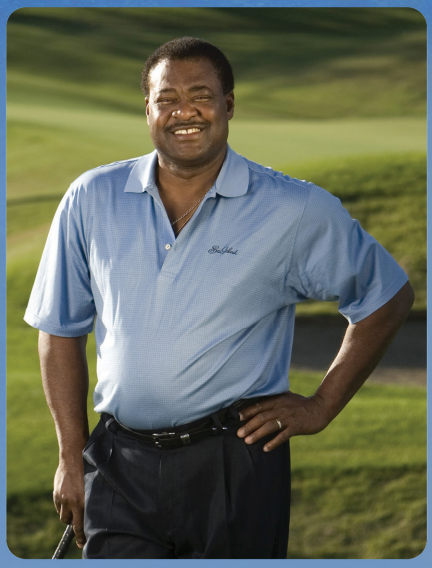

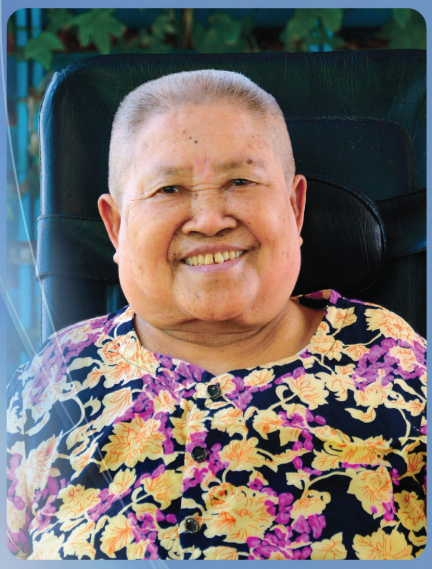

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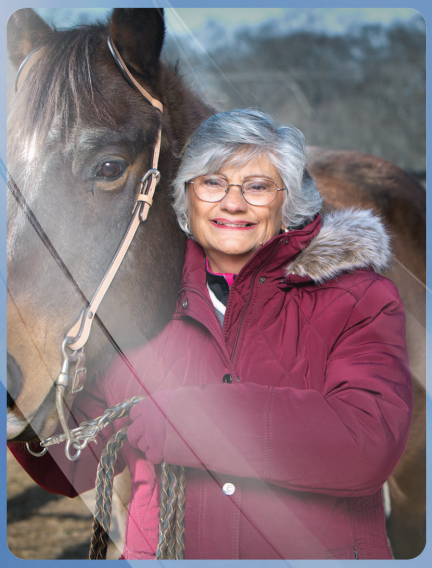
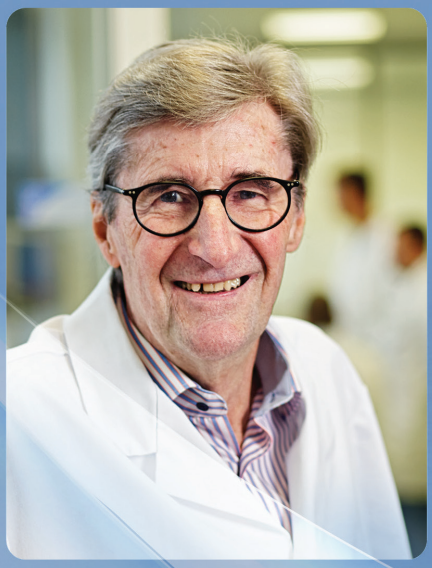
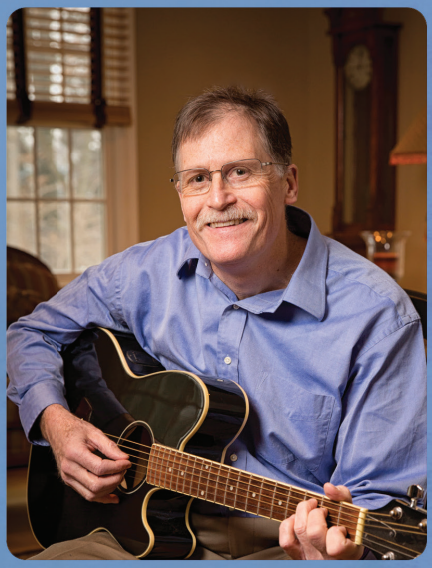

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Updated Analysis of Ocrelizumab Safety in Relapsing and Progressive MS

The safety of ocrelizumab appears stable across multiple studies.

Ludwig Kappos, MD

NEW ORLEANS—The safety profile of ocrelizumab in ongoing open-label extension studies in relapsing multiple sclerosis (MS) and primary progressive MS is generally consistent with that observed in controlled clinical trials, according to a report presented at the 31st Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC). "A slight increase in the rate of serious infections was observed in patients with relapsing MS beyond two years, but the rates remained low," reported Ludwig Kappos, MD, Chair of Neurology at University Hospital Basel in Switzerland, and colleagues. "This was not observed in patients with primary progressive MS, and additional exposure data are needed to determine if the risk increases with further dosing," the researchers said. "Incidence rates of malignancies and breast cancer observed with ocrelizumab treatment in MS remain within the range of epidemiologic background data."

The safety and efficacy of ocrelizumab previously have been characterized in a phase II study in patients with relapsing-remitting MS and in phase III studies in patients with relapsing MS (OPERA I and OPERA II) and in patients with primary progressive MS (ORATORIO). Results from these trials showed that ocrelizumab reduced clinical and MRI evidence of disease activity, compared with placebo and interferon beta-1a. The most common adverse events associated with ocrelizumab during the double-blind periods of the phase III trials included infusion-related reactions, nasopharyngitis, upper respiratory tract infections, headache, and urinary tract infections. During the double-blind treatment period in the phase III trials in relapsing MS, serious adverse events, serious infections, and malignancies were reported in 6.9%, 1.3%, and 0.5% of ocrelizumab-treated patients, respectively (vs 8.7%, 2.9%, and 0.2% of patients treated with interferon beta-1a). In the phase III trial in primary progressive MS, these events were reported in 20.4%, 6.2%, and 2.3% of ocrelizumab-treated patients (vs 22.2%, 5.9%, and 0.8% of patients who received placebo). Across studies, few patients who received ocrelizumab (in the range of 2% to 4%) had adverse event–related treatment withdrawals.

At the CMSC annual meeting, data from controlled and open-label extension periods of the clinical trials of ocrelizumab in relapsing-remitting MS, relapsing MS, and primary progressive MS were presented.

Upon completion of a double-blind treatment period, patients from all studies were eligible to enter a long-term open-label extension in which they received ocrelizumab treatment. Safety analyses were based on integrated data from the phase II and phase III studies. The primary analysis was based on the clinical cutoff dates of the individual studies (phase II, January 22, 2015; OPERA I, April 2, 2015; OPERA II, May 12, 2015; ORATORIO, July 24, 2015). The present updated analysis includes all patients who received one or more dose of ocrelizumab during the controlled or open-label periods of the phase II and phase III studies (ie, the ocrelizumab all-exposure population) as of January 20, 2016. Additional data cutoffs of June 30, 2016, and September 15, 2016, were presented for malignancies to demonstrate changes with increasing ocrelizumab exposure.

The ocrelizumab all-exposure group included 2,279 patients. Patients' mean age was 40.1, and 61.3% were female. Time since MS symptom onset was 6.67 years, and time since MS diagnosis was 3.66 years.

Overall Adverse Events

As of January 20, 2016, the majority (81%) of patients who received ocrelizumab experienced at least one adverse

Updated Analysis of Ocrelizumab Safety in Relapsing and Progressive MS

continued

event, corresponding to a rate of 242 events per 100 patient-years. The most common adverse events included nasopharyngitis, upper respiratory tract infection, urinary tract infection, infusion-related reactions, and headache. Serious adverse events were reported in 12% of patients, corresponding to 6.97 events per 100 patient-years, and most commonly included infections. Treatment withdrawal because of an adverse event occurred in 3.3% of patients (rate, 1.40 per 100 patient-years) and primarily included infusion-related reactions (0.9%) and events coded as neoplasms (0.6%) or infections (0.4%).

Infections

As of January 20, 2016, 56.9% of the ocrelizumab all-exposure population reported one or more infection with ocrelizumab, corresponding to a rate of 73.6 per 100 patient-years. "These findings are consistent with the 75.6 rate observed at the primary analysis cutoff date," the researchers reported. Infections were reported at the highest rate following the first dose and declined with subsequent dosing. Infections reported in 5% or more of patients included nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, and influenza. In the ocrelizumab all-exposure population, the rate per 100 patient-years of serious infections (1.80) as of January 20, 2016, was comparable with the rate at the primary analysis cutoff date (1.74). Data for the pooled relapsing MS population showed a slight increase in the rate per 100 patient-years of serious infections (1.45) as of January 20, 2016, compared with the rate at the primary analysis cutoff date (1.08); "however, rates remained low, and further exposure is needed to make any interpretation," the researchers said.

Among patients with primary progressive MS, the rate per 100 patient-years of serious infections remained stable (2.74) as of January 20, 2016, compared with the rate at the primary analysis cutoff date (2.97). The most common serious infection reported was pneumonia. No infections were identified as opportunistic in nature.

Malignancies

In the MS clinical trial program, an imbalance in the crude incidence of malignancies was observed between the ocrelizumab- and comparator-treated patients, which was associated with a cluster of breast cancer events in the ocrelizumab group. Over time, the crude incidence rate of malignancy per 100 patient-years in the ocrelizumab all-exposure population fluctuated but remained within the epidemiologic range of patients with MS. An observed change in the crude incidence rate of malignancy from June to September is attributed to the crude incidence rate of nonmelanoma skin cancer, which increased from 0.090 at the primary analysis cutoff date to 0.145 at the September 15, 2016, data cutoff, due to six new cases of basal cell carcinoma. The crude incidence rate of breast cancer remained stable through the September 15, 2016, data cutoff.

In More Recent News

In late May 2017, Genentech, the maker of ocrelizumab, notified physicians of the first case of progressive multifocal leukoencephalopathy (PML) in a patient taking ocrelizumab. The case occurred in a JCV-positive patient in Germany who stopped taking natalizumab in February after being on the drug for three years, and received the first dose of ocrelizumab in April. It is unclear whether the PML stemmed from the prior natalizumab treatment or if the switch to ocrelizumab played a role. ■

Siponimod Reduces Risk of Confirmed Disability Progression in Secondary Progressive MS

The treatment also may reduce annualized relapse rate and the number of new lesions.

BOSTON—Siponimod reduces the risk of three-month and six-month confirmed disability progression in patients with secondary progressive multiple sclerosis (MS), according to research described at the 69th Annual Meeting of the American Academy of Neurology. The treatment also appears to reduce relapse rate and the number of new lesions. The study is "the largest controlled double-blind study in secondary progressive MS," according to Ludwig Kappos, MD, Chair of Neurology at University Hospital Basel in Switzerland.

Siponimod is a selective sphingosine 1-phosphate receptor-1 and -5 modulator with effects on the CNS and the peripheral nervous system. The treatment may have effects related to remyelination and neuroprotection, according to Dr. Kappos. He and his colleagues conducted a randomized, double-blind, placebo-controlled, phase III study to compare the effects of siponimod and placebo in patients with secondary progressive MS. The investigators randomized patients 2:1 to once-daily siponimod (2 mg) or placebo. Patients were treated for as long as three years in the double-blind phase of the study. In a subsequent extension study, participants were treated for as long as seven years.

The event- and exposure-driven study's primary end point was time to three-month confirmed disability progression, as assessed by the Expanded Disability Status Scale (EDSS). Key secondary end points included time to confirmed worsening of 20% or more from baseline in the Timed 25-Foot Walk test (T25FW) and T2 lesion volume change from baseline. Other secondary end points included six-month confirmed disability progression, annualized relapse rate, 12-item MS Walking Scale (MSWS-12), number of T1 gadolinium-enhancing and T2 lesions, and percent brain volume change.

The investigators randomized 1,651 patients. The population's mean age was 50, and mean EDSS score was 5.5. The sample was typical of the population of patients with secondary progressive MS.

Siponimod reduced the risk of three-month confirmed disability progression by 21% versus placebo. Dr. Kappos and colleagues consistently observed point estimates in favor of siponimod across predefined subgroups, including patients with no relapses in the two years before study initiation and patients without gadolinium-enhancing lesions at baseline.

Siponimod reduced the annualized relapse rate by 55.5%, the number of T1 gadolinium-enhancing lesions by 86.6%, and the number of new T2 lesions by 81%. The relative differences in change from baseline in T2 lesion volume, MSWS-12, and percent brain volume change were 79.1%, 39.7%, and 23.4%, respectively, versus placebo.

The risk reduction observed for the T25FW was 6.2%, but was not statistically significant. Siponimod reduced the risk of six-month confirmed disability progression by 26%. In addition, siponimod reduced the annualized relapse rate by 55.5%, the number of T1 gadolinium-enhancing lesions by 86.6%, and the number of new T2 lesions by 81%. The relative differences in change from baseline in T2 lesion volume, MSWS-12, and percent brain volume change were 79.1%, 39.7%, and 23.4%, respectively, versus placebo. Siponimod's effects were more pronounced in patients with relapses at baseline, compared with those without, said Dr. Kappos. ■

—Erik Greb

Phase II Data Show Safety and Efficacy of Ozanimod for Relapsing MS

Data from the blinded extension portion of the phase II RADIANCE Part A trial demonstrate the long-term safety and efficacy of ozanimod.

Brett E. Skolnick, PhD

NEW ORLEANS—Ozanimod demonstrated durable efficacy with a favorable safety profile in patients continuing ozanimod for 120 weeks or switching from placebo to ozanimod for 96 weeks, according to results of a phase II study presented at the 31st Annual Meeting of the Consortium of Multiple Sclerosis Centers. "These data support the ongoing RADIANCE and SUNBEAM phase III studies," said Brett E. Skolnick, PhD, on behalf of his study collaborators. Dr. Skolnick is an employee of Receptos, a wholly owned subsidiary of Celgene, in San Diego.

Ozanimod, an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate (S1P) receptor-1 and -5 , is in development for relapsing multiple sclerosis (MS). "The increased receptor selectivity of ozanimod and additional pharmaceutical properties may result in a more favorable safety profile versus other nonselective and selective S1P receptor modulators," said Dr. Skolnick.

In the completed RADIANCE Part A phase II trial, patients with relapsing MS were randomized (1:1:1) to once-daily ozanimod 0.5 mg or 1.0 mg or to placebo for 24 weeks. At week 24, patients could enter a 96-week, blinded extension phase. Patients randomized to ozanimod continued their assigned dose; 85 patients received 0.5 mg, and 81 patients received 1.0 mg. Patients administered placebo were re-randomized (1:1) to ozanimod 0.5 mg (n = 41) or 1.0 mg (n = 42). Ozanimod was dose-escalated over seven days to attenuate first-dose effects.

Approximately 89% of patients taking the 0.5-mg dose and 90% of patients taking the 1.0-mg dose completed the extension study. At week 120, 89% to 91% of patients were free of gadolinium-enhancing lesions. Unadjusted annualized relapse rates were 0.31 in the 0.5-mg group and 0.18 in the 1.0-mg group. One or more treatment-emergent adverse events were seen in 79% of patients taking the 0.5-mg dose and in 76% of those taking the 1.0-mg dose. The most common adverse events were increased alanine aminotransferase (ALT) levels, nasopharyngitis, and upper respiratory tract infection. Serious treatment-emergent adverse events were seen in 12 patients in the 0.5-mg group and in nine patients in the 1.0-mg group. Mild blunting of the normal diurnal heart rate was observed. The largest mean decrease in heart rate relative to pre-dose was 3.5 bpm at hour 6 on day 1, with no associated symptoms. No type II or 2:1 atrioventricular block was reported.

At week 120, ALT levels were three or more times the upper limit of normal in 6% of the 0.5-mg group and in 7% of the 1.0-mg group. In the 0.5-mg group, 2% of patients discontinued ozanimod due to increased liver transaminases. Less than 1% of patients in the 1.0-mg group discontinued ozanimod for the same reason. Between baseline and week 120, three patients in the 1.0-mg group had absolute lymphocyte counts below 200 cells/μL; none was associated with severe or serious infection. There were no notable cases of pulmonary adverse events and no cases of macular edema, malignancy-related adverse events, or serious opportunistic infections.

This study was supported by Celgene. ■

SUGGESTED READING

Cohen JA, Arnold DL, Comi G, et al. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15(4):373-381.

Pooled Data Show Benefits of Cladribine Tablets on Relapse Rates and Disability Progression in Patients With MS

Gavin Giovannoni, MBBCh, PhD

Analysis of pooled data show benefit over placebo.

NEW ORLEANS—Analysis of pooled data from the CLARITY and ONWARD studies showed that cladribine tablets 3.5 mg/kg decreased annualized relapse rate by 57% and reduced the risk for six-month confirmed disability progression by 39% versus placebo in a population of patients with active relapsing multiple sclerosis (MS). These findings were presented at the 31st Annual Meeting of the Consortium of Multiple Sclerosis Centers.

Treatment with cladribine tablets in the CLARITY and ONWARD studies demonstrated efficacy versus placebo across a range of patients with active MS. "Combining efficacy data from the double-blind periods of these studies allows assessment of the efficacy of two years' treatment with cladribine tablets 3.5 mg/kg," said Gavin Giovannoni, MBBCh, PhD, on behalf of his research colleagues. Dr. Giovannoni is a Professor at the Blizard Institute at Barts and the London School of Medicine and Dentistry in London.

Dr. Giovannoni and colleagues used pooled data from the two-year, double-blind periods of CLARITY and ONWARD to analyze the efficacy of cladribine tablets 3.5 mg/kg in patients with relapsing MS (n = 1,067) and in subgroups defined by baseline characteristics. Patients from ONWARD on cladribine tablets or placebo were also taking interferon beta. Annualized relapse rates and three-month and six-month confirmed disability progression were compared using relative risk ratios from a Poisson regression model, hazard ratios from a Cox proportional hazard model, and 95% confidence intervals for patients treated with cladribine tablets 3.5 mg/kg or placebo. The subgroups analyzed included, among others, patients with no T1 gadolinium-enhancing lesions (n = 759) or one or more T1 gadolinium-enhancing lesions (n = 308) and patients with an Expanded Disability Status Scale (EDSS) score of 3.0 or lower (n = 653) or 3.5 or greater (n = 414).

For annualized relapse rate, consistent benefits were seen with cladribine tablets 3.5 mg/kg versus placebo in the overall population (relative risk ratio: 0.43) and in the subgroups.

For annualized relapse rate, consistent benefits were seen with cladribine tablets 3.5 mg/kg versus placebo in the overall population (relative risk ratio: 0.43) and in the subgroups: no T1 gadolinium-enhancing lesions, 0.46; one or more T1 gadolinium-enhancing lesions, 0.38; EDSS of 3.0 or lower, 0.40; EDSS of 3.5 or greater, 0.47. Benefits favored cladribine tablets 3.5 mg/kg versus placebo in the overall population for time to three-month confirmed disability progression (hazard ratio: 0.64) and six-month confirmed disability progression (hazard ratio: 0.61) and in each of these outcomes in a majority of subgroups. For three-month confirmed disability progression: no T1 gadolinium-enhancing lesions, hazard ratio: 0.59; one or more T1 gadolinium-enhancing lesions, hazard ratio: 0.75; EDSS of 3.0 or lower, hazard ratio: 0.76; EDSS of 3.5 or greater, hazard ratio: 0.55. For six-month confirmed disability progression: no T1 gadolinium-enhancing lesions, hazard ratio: 0.59; one or more T1 gadolinium-enhancing lesions, hazard ratio: 0.66; EDSS of 3.0 or lower, hazard ratio: 0.75; EDSS of 3.5 or greater, hazard ratio: 0.51.

This study was supported by EMD Serono. ■

Preliminary Study Suggests Possible New Treatment for Progressive MS

Autologous EBV-specific T cells may be a potential treatment for patients with progressive MS.

Michael P. Pender, MD, PhD

BOSTON—Interim results from a small, preliminary study support a new type of treatment for progressive multiple sclerosis (MS). Results from the first six people enrolled in the phase I study, which was designed to enroll 10 people, were presented at the 69th Annual Meeting of the American Academy of Neurology. "While these results are very preliminary, and much more research is needed, we are excited there were no serious side effects," said study author Michael P. Pender, MD, PhD, a Professor and Director of the MS Research Group at the University of Queensland in Brisbane, Australia.

The study investigated the relationship between MS and the Epstein-Barr virus (EBV). Previous research has suggested a role for EBV in MS pathogenesis. The study involved six people with progressive MS who had moderate to severe disability (ie, Expanded Disability Status Scale scores between 5.0 and 8.0).

In some people with MS, EBV-infected autoreactive B cells might accumulate in the CNS because of defective cytotoxic CD8+ T-cell immunity. Elimination of EBV-infected B cells may reduce the destruction of myelin in MS.

For the study, researchers removed the participants' own T cells and stimulated them to boost their ability to recognize and destroy cells infected with EBV. They then injected participants with infusions of escalating doses of T cells every two weeks for six weeks. They followed the patients for 26 weeks to look for evidence of side effects and possible improvement of symptoms.

Three participants showed symptomatic and objective clinical improvement, starting two to eight weeks after the first infusion.

"One person with secondary progressive MS showed striking improvement," Professor Pender said. This participant had normalization of lower extremity tone and plantar responses for the first time in 16 years. "This participant had a significant increase in ambulation from 100 yards with a walker at the start of the study, and over the previous five years, to three quarters of a mile, and was now also able to walk shorter distances with only one-sided assistance. Lower leg spasms that had persisted for years resolved."

Professor Pender said that another participant with primary progressive MS had reduced fatigue, increased productivity, and improved balance. Another responder had improved color vision, visual acuity, and manual dexterity; reduced fatigue; fewer lower extremity spasms; and less urinary urgency. All three responding participants had improvements in fatigue and ability to perform daily activities.

"The best responses were seen in the two people who received T cells with the highest amount of reactivity to the EBV," Professor Pender said. None of the six participants had serious side effects.

"Much more research needs to be done with larger numbers of participants to confirm and further evaluate these findings," Professor Pender said. "But the results add to the mounting evidence for a role of the Epstein-Barr virus infection in MS and set the stage for further clinical trials."

The study was a collaboration between the QIMR Berghofer Medical Research Institute, Royal Brisbane and Women's Hospital, and the University of Queensland. The study was supported by MS Queensland, MS Research Australia, QIMR Berghofer Medical Research Institute, and Perpetual Trustee Company Limited.

—*Glenn S. Williams*

SUGGESTED READING

Pender MP, Csurhes PA, Smith C, et al. Epstein-Barr virus-specific adoptive immunotherapy for progressive multiple sclerosis. *Mult Scler.* 2014;20(11):1541-1544.

Alemtuzumab May Prevent MRI Lesions for Six Years in Patients With Highly Active Disease

The majority of patients were free of gadolinium-enhancing T1 lesions and new or enlarging T2 hyperintense lesions.

Anthony Traboulsee, MD

NEW ORLEANS—Most patients with relapsing-remitting multiple sclerosis (MS) with highly active disease remain free of new MRI activity for six years after receiving alemtuzumab, according to research presented at the 31st Annual Meeting of the Consortium of MS Centers. The durable effects may result from the distinct pattern of lymphocyte repopulation following treatment with alemtuzumab, which may lead to a rebalancing of the immune system, said Anthony Traboulsee, MD, Associate Professor of Neurology at the University of British Columbia in Vancouver. Additional mechanistic studies are needed to establish this hypothesis, the authors said.

To evaluate six-year MRI and brain volume loss outcomes in a subset of patients with highly active disease at baseline who were treated with alemtuzumab, Dr. Traboulsee and colleagues analyzed data from the CARE-MS I trial. In that trial, researchers randomized patients with active relapsing-remitting MS who were drug-naïve at baseline to alemtuzumab or interferon beta-1a. After two years, patients who received alemtuzumab had improved clinical and MRI outcomes, including brain volume loss, compared with patients who received interferon beta-1a. In addition, significantly more of these patients had no evidence of disease activity, compared with patients treated with interferon beta 1-a.

In an extension study, patients could receive additional treatment with alemtuzumab (12 mg/day on three consecutive days at one year or more after the most recent course) as needed for relapse or radiologic activity. During the extension, patients also could receive treatment with other licensed disease-modifying therapies at an investigator's discretion. Retreatment criteria included one or more relapse, two or more new or enlarging T2 hyperintense lesions, or new gadolinium-enhancing T1 brain or spinal cord lesions on MRI. Researchers defined highly active disease as two or more relapses a year prior to randomization and one or more gadolinium-enhancing T1 lesion at core study baseline.

The researchers obtained MRI scans at baseline and yearly thereafter. Experts masked to patients' original treatment group assignment analyzed the MRI scans. Investigators assessed the proportion of patients free of MRI disease activity (ie, no new or enlarging T2 hyperintense lesions or new gadolinium-enhancing T1 lesions) and the proportion of patients free of new non-enhancing T1 lesions. Brain volume loss was derived from brain parenchymal fraction change.

Of 376 patients who received alemtuzumab in the CARE-MS I trial, 105 met the criteria for highly active disease at core study baseline. Of these 105 patients, 99 remained in the study through Year 6. Through six years, 63% of patients did not receive additional treatment with alemtuzumab or another disease-modifying therapy. In each year through Year 6, a majority of patients were free of MRI disease activity (61% at Year 6), free of new gadolinium-enhancing T1 lesions (83% at Year 6), and free of new or enlarging T2 hyperintense lesions (62% at Year 6). The investigators also observed that annually in Years 2 through 6, high proportions of patients had no new non-enhancing T1 hypointense lesions.

"These findings, along with long-term clinical efficacy, suggest that alemtuzumab may provide a unique treatment approach for relapsing-remitting MS patients with highly active disease, offering durable efficacy in the absence of continuous treatment," said Dr. Traboulsee and colleagues. ■

Preliminary Results Suggest Ublituximab Is Safe in Relapsing MS

Researchers observed rapid and robust B-cell depletion in a phase II study.

Amy Lovett-Racke, PhD

NEW ORLEANS—Ublituximab, a novel glycoengineered anti-CD20 antibody, is well tolerated and demonstrates rapid and robust B-cell depletion, according to a report presented at the 31st Annual Meeting of the Consortium of Multiple Sclerosis Centers. "Unlike other anti-CD20s, ublituximab can be delivered in shorter infusions, providing a convenience benefit for patients," reported Amy Lovett-Racke, PhD, and her research colleagues. Dr. Lovett-Racke is a Professor in the Department of Microbial Infection and Immunity at Ohio State University Medical Center in Columbus.

Patients with relapsing or primary progressive forms of multiple sclerosis (MS) have shown significant clinical improvement after B-cell depletion with an anti-CD20 antibody. Ublituximab is a chimeric monoclonal antibody that targets a unique epitope on the CD20 antigen. It has been glycoengineered to enhance affinity for all variants of FcgRIIIa receptors, demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab. Ublituximab is currently in phase III trials for the treatment of hematologic malignancies.

To determine the level of B-cell depletion by ublituximab in subjects with relapsing MS, Dr. Lovett-Racke and colleagues conducted a 52-week, phase II, placebo-controlled, multicenter study that was designed to assess the infusion time and optimal dose as well as the safety and tolerability of ublituximab in patients with relapsing MS. The investigators also performed radiologic and clinical analyses. Optimal dosing was determined by B-cell depletion, defined as percentage of CD19+ B cells present following ublituximab administration. This percentage was calculated by gating the entire lymphocyte/myeloid population. Within this population, CD19+ CD3– cells were gated, and the percentage of CD19+ B cells was determined.

> "Unlike other anti-CD20s, ublituximab can be delivered in shorter infusions, providing a convenience benefit for patients."

To date, B-cell data from 11 subjects have been analyzed up to week four of the 52-week study, encompassing two infusions of ublituximab. No severe adverse events have been reported, including in subjects receiving rapid infusions. Only patients whose B-cell levels were within a normal range (≥ 5% of total lymphocytes) at screening were included in the study. At week four (one week post second infusion), median B-cell depletion was 99% from baseline in ublituximab-treated subjects, while controls maintained similar B-cell levels, as compared with baseline.

This study was supported by TG Therapeutics. ■

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