

Findings in the Field of Multiple Sclerosis

Headache Occurrence

Although headache is a rare symptom at the time of onset of multiple sclerosis (MS), it is common in patients with established disease, according to Chiara Monaldini, University of Ferrara, Ferrara, Italy. Headache prevalence varies widely across different forms of MS, but not by type of therapy.

Among 135 consecutive patients who visited the MS center in Ferrara during a 5-month period, 3% had clinically isolated syndrome, 83.7% had relapsing-remitting MS, 1.5% had primary-progressive disease, and 11.8% had secondary-progressive disease. A total of 77% of patients presented with headache according to the criteria of the International Headache Society. The lifetime prevalence was 52% for migraine and 37% for tension-type headache. Treatment for MS consisted of interferon- β in 45% of patients, glatiramer acetate in 21%, and other therapies in 8%. A total of 26% of patients were untreated. The frequency of headache did not differ in these groups. Based on the findings of a higher frequency of headache in MS than in the general population (**Editor's Note:** *This study did not use a concurrent control group.*), the investigators hypothesized that a possible association may exist between the two pathologies.

Outcomes Overview

The effects of disease-modifying therapies (DMTs) on clinical and economic outcomes in patients with MS were addressed in several analyses.

Qian Cai, HealthCore Inc., Wilmington, Delaware, reported that second-line therapy with natalizumab reduced healthcare resource utilization and cost of care in patients with MS. This conclusion was based on a "real-world" analysis of administrative claims data from 14 commercial health plans across the United States, covering 178 patients <65 years old who received natalizumab at least once between July

1, 2004, and June 30, 2008. The all-cause cost of medical services (including hospitalization, emergency department visits, physician office visits, other outpatient visits, and infusion costs) was \$19,723 per year when the patients were receiving their first-line therapy and \$14,250 per year after they switched to natalizumab ($P<0.01$). The data were also analyzed with respect to relapse-related health care resource utilization, which was defined as either a claim for an MS-related hospitalization or a claim for an MS-related outpatient visit in combination with a pharmacy or medical claim within 7 days after the visit for intravenous (IV) methylprednisolone, IV corticotropin, or oral methylprednisolone, prednisone, prednisolone, or dexamethasone. The annual cost for MS-related medical services decreased from \$15,237 during first-line therapy to \$9,469 during second-line natalizumab treatment ($P<0.01$). Acute MS-related health care encounters also became significantly less frequent, totaling 2.78 per year during first-line treatment vs 1.25 per year during treatment with natalizumab ($P<0.01$).

Hiangkiat Tan, HealthCore Inc., Wilmington, Delaware, described an analysis from the same administrative claims database showing that MS patients who adhered to treatment experienced significantly better clinical and economic outcomes. The study focused on 2,446 MS patients who had received 1 or more first-line DMT between July 1, 2004, and June 30, 2008. Adherence was evaluated using a medication possession ratio (MPR), which was defined as the total number of days of supply of the index treatment (the first DMT received) divided by a 1-year period. Patients with an MPR $\geq 80\%$ were considered adherent. Adherence to the index medication was confirmed in 54.6% of the study population. Nonadherent patients were significantly more likely to have an MS-related hospitalization or MS-related emergency department visit, as well as greater

relapse-related health care resource utilization, when compared with adherent patients. On multivariate analysis, the odds ratios in nonadherent patients were 1.70 (95% confidence interval [CI], 1.28 to 2.26) for MS-related hospitalization, 1.49 (95% CI, 1.12 to 1.98) for MS-related emergency department visits, and 1.71 (95% CI, 1.43 to 2.05) for relapse-related health care resource utilization. Adjusted MS-related medical costs during the 1-year follow-up period were 40% higher in nonadherent than adherent patients (\$4,485 vs \$3,199, respectively; $P<0.001$).

Paolo Gallo, Multiple Sclerosis Centre, University Hospital, Padua, Italy, reported that DMTs significantly reduced the development of new inflammatory cortical lesions (CLs) in a study of 150 patients with relapsing-remitting MS. After 12 months of therapy, magnetic resonance imaging revealed new CLs in 45% of patients randomized to either subcutaneous or intramuscular interferon β -1a, interferon β -1b, or glatiramer acetate, compared with 74% in an untreated reference population ($P<0.001$). At 24 months, the difference remained significant, with new CLs identified in 64% of the combined treatment groups and 82% of the untreated group ($P<0.001$). New CLs were significantly less common with subcutaneous interferon β -1a than with the other DMTs at 12 months, but no between-treatment differences were evident at 24 months. Immunomodulatory therapy also reduced the number of new white matter lesions, with a rate of 45.8% in the combined treatment groups compared with 54.0% in the untreated group at 24 months ($P<0.001$).

Various reports at the AAN described changes in the use of DMTs and predictors of response to such treatments for MS.

The use of DMTs rose by approximately 50% in Canada between 2002 and 2007, according to a retrospective cohort analysis of population-based data presented by Dalia L. Rotstein,

St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. Based on population data from International Medical Statistics, the total annual number of prescriptions for subcutaneous or intramuscular interferon β -1a, interferon β -1b, and glatiramer acetate increased from 3.9 to 5.1 per 1,000 Canadians. The total annual cost of DMT prescriptions increased by approximately 30%, from CAN\$187 million to CAN\$287 million. The most commonly used DMT was subcutaneous interferon β -1a, but glatiramer acetate was associated with the greatest growth in use. Patterns of DMT use varied markedly across the various Canadian provinces, likely because of factors such as differences in patient eligibility for prescription coverage and the extent of such coverage. Natalizumab was not covered by government funding during this period and was used in insignificant quantities.

Long-term data from an extension of a double-blind trial suggest that the efficacy of maintenance therapy with glatiramer acetate is enhanced when preceded by brief immunosuppression with mitoxantrone in patients with relapsing-remitting MS. Timothy Vollmer, University of Colorado Health Sciences Center, Aurora, Colorado, explained that this 15-month, double-blind trial revealed a decrease in the number of new gadolinium-enhancing lesions, T2-weighted lesion volume accumulation, and evolution of gadolinium-enhancing lesions to T1 black holes in patients who received mitoxantrone induction (monthly infusions of 12 mg/M² for 3 months) followed by daily glatiramer acetate maintenance therapy (20 mg/d) compared to those who received glatiramer acetate alone. The superior benefits of the induction regimen were sustained in a 21-month, open-label extension study. The analysis presented by Dr. Vollmer represented findings at 60 months, a point at which 13 of 15 patients in the induction group and 12 of 15 in the noninduction group remained in the study. The proportion of gadolinium-enhancing lesions occurring during the study that had converted to T1 black holes

was significantly lower among patients who had received mitoxantrone induction compared with those who had received only the glatiramer acetate maintenance regimen (15% vs 45%, respectively; $P=0.042$). No significant differences were evident between the groups with regard to other magnetic resonance imaging (MRI) parameters (such as brain atrophy, volume of T1 lesions, and proportion of gadolinium-enhancing lesions at screening that

Patients nonadherent to DMT were significantly more likely to have an MS-related hospitalization or emergency department visit, as well as greater relapse-related health care resource utilization, as compared with their adherent counterparts.

converted to T1 black holes), although a trend favoring mitoxantrone induction was observed with respect to change in T2 lesion volume (mean change was -0.848 for the induction group and 0.59 for the noninduction glatiramer acetate group; $P=0.06$). The proportion of patients free from relapse was 83% in the induction group and 61% in the noninduction group, and the changes in Expanded Disability Status Scale scores from baseline to 60 months were 0.14 and 0.24 for the two groups, respectively (no significant differences between the groups for either measure). Brief immunosuppression with mitoxantrone prior to glatiramer acetate maintenance therapy resulted in sustained differences in MRI measures of disease activity and burden of disease, concluded Dr. Vollmer, who noted that a majority of patients in both groups remained relapse free and demonstrated little worsening in disability.

Treatment Pharmacology

A selective sphingosine 1-phosphate (S1P) receptor-1 modulator, the oral

prodrug CS-0777, has been found to cause pronounced, dose-dependent reductions in peripheral blood lymphocytes, total T cells, CD4 and CD8 T cells, and B cells, noted Hamim Zahir, Daiichi-Sankyo, Edison, New Jersey. These effects are similar to those of other S1P modulators, but CS-0777 also appears to produce a dose-dependent decrease in CD4 effector memory T cells, unlike fingolimod, while relatively sparing CD8 effector memory T cells. These observations came from a study in which patients with MS received CS-0777 in increasing doses: 0.1, 0.3, and 0.6 mg once weekly or every other week for 12 weeks. Decreases in CD4 T cells were greater than those in CD8 T cells, with a consequent reduction in the CD4:CD8 ratio. Naïve and central memory CD4 and CD8 T cells decreased to similar extents, as did naïve and memory B cell subsets. The effect on B cells was somewhat more pronounced than the effect on T cells, especially with lower doses of CS-0777, suggesting that B-cell trafficking might be more sensitive to the agent. The administration of CS-0777 did not affect natural-killer (NK) cells, but resulted in a transient, dose-related reduction in NK T cells. The investigators suggested that further investigation is warranted to clarify the clinical implications of these findings.

The results of the CopImmunoNet Study have shown that glatiramer acetate appears to be an effective “platform drug” that can be used independently of pretreatments with interferon- β , mitoxantrone, or natalizumab. Nina Kleiner, Dresden University of Technology, Dresden, Germany, explained that no immunological differences were apparent between MS patients who received glatiramer acetate as initial therapy as opposed to patients who switched to glatiramer acetate from other treatments. Among the patients who started treatment with glatiramer acetate in this prospective, multicenter trial, 32 were given the drug as initial therapy, 19 switched from interferon- β , 5 de-esca-

CONTINUED ON PAGE 6

Findings in the Field of Multiple Sclerosis

CONTINUED FROM PAGE 5

lated from mitoxantrone, and 4 switched from natalizumab. During the subsequent year, there were no significant differences between these groups with regard to the decrease in proliferation of peripheral blood leukocytes with glatiramer acetate, which was evident 3 months after initiation of this therapy. A Th1–Th2 shift was documented in all patients at month 6, regardless of the type of pretreatment they received. No significant differences in serum antibodies to glatiramer acetate were found across treatment groups.

Oral Therapies

Mark Freedman, University of Ottawa, Ottawa, Ontario, Canada, reported that the addition of oral teriflunomide to patients on stable therapy with subcutaneous glatiramer acetate raised no safety concerns in a 6-month analysis of data from an ongoing 1-year efficacy trial in patients with relapsing-remitting MS. Patients on glatiramer acetate for at least 6 months, who had not experienced relapses during the 4 weeks preceding study enrollment, were randomized to receive oral teriflunomide 7 mg/d (n=37) or 14 mg/d (n=34) or placebo (n= 39) for 24 weeks. Treatment-emergent adverse events (TEAEs) led 7 patients to discontinue the study (3 patients in the teriflunomide 7 mg/d group and 4 patients in the teriflunomide 14 mg/d group). Abnormalities in liver function tests, which have been a focus of attention with teriflunomide, were relatively low; TEAEs due to increased alanine aminotransferase (ALT) activity were experienced by 6 patients (2 per treatment group), and 2 patients (1 on placebo and 1 on teriflunomide 14 mg/d) had ALT levels 3 times greater than the upper limit of normal. No TEAEs potentially related to immunosuppression, including white blood cell counts, and infections, led to study discontinuation, and the proportion of patients with these

TEAEs was balanced across the treatment groups: 44%, 43%, and 38% for placebo, teriflunomide 7 mg/d, and teriflunomide 14 mg/d, respectively. Additionally, some patients who had refractory lesions on glatiramer acetate monotherapy experienced suppression of these lesions after teriflunomide was added. Compared to placebo, the number of T1-weighted gadolinium-enhanced lesions were significantly reduced in the teriflunomide 7 mg/d group ($P=0.011$), and T1 gadolinium-enhanced lesion volume was significantly reduced in the 14 mg/d group ($P=0.039$). Dr. Freedman noted that further data are required to establish the clinical benefit and safety of combination therapy with teriflunomide and glatiramer acetate and to determine whether efficacy with the combination is greater than with either agent alone.

Investigators called for larger-scale analyses to discern the true incidence of prolonged lymphopenia after cessation of fingolimod.

Persistent reductions in circulating lymphocytes after discontinuation of fingolimod therapy for MS were described by Mark R. Keezer, McGill University, Montreal, Quebec, Canada. Data from 2 of 5 patients enrolled in open-label extension phases of fingolimod clinical trials indicated that peripheral lymphocyte counts can remain depressed for prolonged periods following cessation of long-term fingolimod treatment. The analysis focused on 5 females who had received oral fingolimod (1.25 mg/d), all of whom had normal lymphocyte counts (0.8 to $1.2 \times 10^9/L$) at the time of enrollment, per the study protocols. Subsequently, fingolimod treatment was interrupted based on protocol-

defined criteria, including a lymphocyte value $<0.2 \times 10^9/L$, increased liver enzymes, or intercurrent disease. No relapses occurred either during therapy or after the drug was discontinued. Three patients who received fingolimod for 15, 24, and 60 months, respectively, recovered normal lymphocyte counts within 2 months after stopping the drug. In another patient treated for 60 months, however, lymphocyte values remained below normal ($0.4 \times 10^9/L$) at the last follow-up, 6 months after treatment was stopped. The fifth patient discontinued fingolimod after 38 months when she developed a lung lesion, which was resected 1 month later. Her lymphocyte count was $0.4 \times 10^9/L$ at the time of resection and remained depressed ($0.7 \times 10^9/L$) 24 months after she stopped fingolimod (the last follow-up). Lymph nodes in the resected tissue (a necrotizing nontuberculous granuloma) were histologically unremarkable. The investigators called for larger-scale analyses to discern the true incidence of prolonged lymphopenia after cessation of fingolimod and to determine whether time to recovery of circulating lymphocytes might be used as a biomarker to guide resumption of therapy.

In addition to exerting immunomodulatory effects, laquinimod appears to contribute to neuroprotection by enhancing levels of brain-derived neurotrophic factor (BDNF) in patients with relapsing-remitting MS, noted Jan Thörne, Ruhr-University Bochum, Bochum, Germany. This observation was the result of an analysis of 596 serum samples from patients with relapsing-remitting MS randomized to laquinimod 0.6 mg/d or placebo in a clinical trial. Treatment with laquinimod resulted in a significant increase of up to 11-fold in BDNF serum levels at 3 and 9 months. At 3 months, the BDNF level in the laquinimod group was $16,088 \pm 760$ pg/mL compared with $12,882 \pm 625$ pg/mL in the placebo group ($P<0.05$). The change in BDNF level

among laquinimod-treated patients was also significant when compared with the baseline level of $14,436 \pm 778$ pg/mL in this group ($P < 0.05$). The effect on BDNF was maintained at 9 months; however, levels of neurotrophin-3 and inflammatory-associated chemokines or cytokines were not altered with laquinimod compared with placebo.

Janet Wang, University of Calgary, Calgary, Alberta, Canada, reported that an important component of the mechanism of therapeutic benefit with laquinimod may be inhibition of the activity of microglia and macrophages. Her work showed that culturing microglia (from the brains of human fetal samples or human adult surgical brain resections) and macrophages (from the peripheral blood of healthy adult volunteers) with lipopolysaccharide (LPS) produced substantial increases in levels of tumor necrosis factor- α (TNF- α), interleukin-10 (IL-10), and matrix metalloproteinase-9 (MMP-9). When laquinimod was added 24 hours before LPS, levels of TNF- α decreased and levels of IL-10 increased in activated microglia. TNF- α decreased in activated macrophages. Levels of MMP-9 in both microglia and macrophages were reduced in the presence of laquinimod. Furthermore, the cell size of microglia was considerably increased during LPS activation—an effect that was blocked by laquinimod in a concentration-dependent fashion. Laquinimod did not affect the total number of microglia or their expression of CD14, an observation that indicates the change in cytokine and MMP-9 levels did not result from nonspecific cellular toxicity. ■