

Oral Therapy Study Outcomes: A Global View

Research into the efficacy and safety of oral therapies for MS continues at a rapid pace worldwide.

Clinical and MRI assessments of continuous treatment with fingolimod 1.25 mg/day have found persistent inhibition of MS disease activity at 3 years. These results were reported by Ludwig Kappos, University Hospital, Basel, Switzerland, and colleagues from an analysis of data on 173 patients who had participated in a 6-month, placebo-controlled trial of this

oral agent. Those subjects originally assigned to placebo were subsequently re-randomized to fingolimod 1.25 or 5.0 mg/day during a 36-month extension, whereas those originally assigned to fingolimod continued their 1.25 mg/day dosage. At months 15 to 24, all patients assigned to fingolimod 5.0 mg/day were switched to 1.25 mg/day because an assessment indicated that the higher dosage offered no efficacy advantage and might have a less favorable safety profile than the lower dosage. The Table shows the 3-year results; most patients (76%–80%) in all groups were also free of 6-month sustained progression of disability at month 36.

A controlled, double-blind study by Giancarlo Comi, University Vita-Salute and Scientific Institute San Raffaele, Milan, Italy, and colleagues, found that patients who received continuous treatment with laquinimod 0.6 and 0.3 mg/day for 18 months showed low disease activity as assessed by MRI. In a

36-week extension of this study, those patients originally assigned to placebo were re-randomized to receive laquinimod 0.6 or 0.3 mg/day, whereas those assigned to laquinimod continued their original treatment. Data from 235 patients showed that the mean number of Gd-enhanced lesions decreased sig-

For more details on laquinimod and MRI outcomes, please see Comi G et al. Effect of laquinimod on MRI-monitored disease activity.... *Lancet*. 2008;371:2085-2092.

nificantly (by 52%; $P < 0.0007$) among those who switched from placebo to laquinimod and that the reduction was significant regardless of whether they received the higher dose ($P < 0.009$) or the lower dose ($P < 0.03$). A significant reduction was also apparent in the

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Abbreviation Key for This Issue

ADEM	acute disseminated encephalomyelitis
CIS	clinically isolated syndrome
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
Gd	gadolinium
IFN	interferon
IM	intramuscular
mITT	modified intention-to-treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
PPMS	primary-progressive multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SC	subcutaneous
SPMS	secondary-progressive multiple sclerosis
VLA	very late antigen
WCTRIMS	World Congress on Treatment and Research in Multiple Sclerosis

Table. Fingolimod 3-Year Findings.

	Continuous Fingolimod Group (1.25 mg/day)	Placebo Crossover Group (5.0/1.25 mg/day)
Annualized relapse rate after 36 months	0.20	0.21
Free from relapse at 36 months (% of patients)	68%	73%
Free from Gd-enhanced lesions at 36 months (% of patients)	88%	89%
Mean number of new T2 lesions	0.7	1.1

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patients initially treated with laquinimod 0.6 mg/d ($P=0.0062$) or 0.3 mg/d ($P=0.0013$) vs placebo.

BG00012 (an oral formulation of dimethyl fumarate) may have a role to play in the preservation of neural tissue in patients with RRMS, noted David G. MacManus, Institute of Neurology, London, United Kingdom. He made this suggestion based on the results of a retrospective study by him and his colleagues of MRI data from 56 patients who were randomized to receive BG00012 or placebo in a phase IIb study. New Gd-enhanced lesions converted to T1-hypointense lesions in 29% of the BG00012 group compared with 44% of the placebo group. The probability of such conversion was significantly lower with BG00012 than with placebo (odds ratio, 0.53; 95% confidence interval, 0.46–0.62; $P<0.0001$).

Hanneke Hulst, VU University Medical Center, Amsterdam, The Netherlands, and colleagues described a post hoc analysis that suggested that oral ibudilast, a nonselective, phosphodiesterase inhibitor that regulates Th1/Th2 cell

balance, has an inhibitory effect on the development of persistent black holes in patients with active relapsing MS. Data were obtained from 297 patients who were randomized to receive ibudilast 30 to 60 mg/day or placebo in a controlled trial. Results at 1 year showed that the

For more details on
BG00012, please see
Kappos L et al. Efficacy
and safety of oral fumarate
in patients with relapsing-
remitting multiple sclerosis....
Lancet. 2008;372:1463–1472.

proportion of active lesions that evolved into persistent black holes were 0.20 and 0.16 for ibudilast 30 and 60 mg/day, respectively, vs 0.24 for placebo. Compared with placebo, ibudilast 60 mg/day was associated with significantly lower relative risk for lesion evolution into persistent black holes (relative risk 0.63; 95% confidence interval, 0.44–0.90; $P=0.011$). The 30-mg/day

dose showed a nonsignificant trend toward lower risk.

Another study of ibudilast suggested that its clinical benefits primarily stem from protection against neuronal damage. The results were reported by Richard Gammans, MediciNova, San Diego, California, and colleagues. This study randomized patients to receive ibudilast 30 or 60 mg/day or placebo for 1 year, after which the placebo group was re-randomized to the 2 ibudilast dosages while the original ibudilast groups continued their original dosages. Data available from 264 patients at 2 years indicated that sustained disability progression (+1 point on the EDSS for ≥ 4 months) was significantly lower in patients continuously treated with ibudilast than in those who switched to ibudilast from placebo (10.4% vs 21%, respectively; $P=0.03$). Furthermore, treatment with the ibudilast 60-mg/day dosage for 2 years was associated with a significant reduction in formation of persistent black holes when compared with the other groups ($P=0.04$). ■

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COREY C. FORD, MD, PhD: Acorda, Berlex, Biogen Idec, BioMS Technology, Cognition Pharmaceuticals, Genentech, Novartis, Pfizer, Protein Design Labs, EMD Serono, Teva Neuroscience/Teva Pharmaceutical Industries.

STEPHEN S. KIRZINGER, MD: Bayer, Biogen Idec, Eisai, Forest Laboratories, Pfizer, Schwarz Pharma, EMD Serono, Teva Neuroscience/Teva Pharmaceutical Industries.

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Examining Emerging Therapies & Approaches

Several reports at the 2008 WCTRIMS meeting offered new data from clinical trials of both investigational and established therapies for MS.

Rituximab in PPMS

Kathleen S. Hawker, Ohio State University, Columbus, Ohio, and colleagues reported on the efficacy and safety of rituximab in PPMS. The study involved 439 patients who were randomized to receive 2 intravenous infusions of rituximab or placebo (each dose separated by 2 weeks) every 24 weeks over a period of 96 weeks (4 treatment courses). The difference in time to confirmed disease progression between the treatment groups was not statistically significant, but the median change in T2 lesion volume from baseline to week 96 was significantly lower with rituximab than with placebo ($P=0.0008$). No significant differences in brain volume were apparent between treatment groups.

Alemtuzumab

Alemtuzumab showed a significant difference from SC IFN β -1a with respect to achieving a clinically disease-free state in a trial of patients with RRMS. Krzysztof Selmaj, Klinika i Katedra

For more details on alemtuzumab and SC IFN β -1a in early MS, please see The CAMMS223 Trial Investigators. Alemtuzumab vs interferon beta-1a in early multiple sclerosis. *N Engl J Med.* 2008;359:1786-1801.

Neurologii Akademii, Lodz, Poland, on behalf of the CAMMS223 Study Group, explained that these findings came from a randomized trial of 334 patients who received SC IFN β -1a 44 μ g 3 times

weekly or alemtuzumab infusions of 24 or 12 mg/day for 5 days at Month 0, 3 days at Month 12, and, in some patients, for 3 days at Month 24. Follow-up data showed that the proportion of patients free from relapse, free from 3-month accumulation of disability, and free from 6-month accumulation of disability was significantly greater with alemtuzumab than with SC IFN β -1a at years 1 through 3 ($P<0.0001$). In addition, the proportion of patients free from clinical disease was significantly higher with alemtuzumab than with IFN β -1a at years 1 (86% vs 63%, respectively), 2 (81% vs 48%, respectively), and 3 (71% vs 38%, respectively); $P<0.0001$ for all comparisons.

Alternate-Day Dosing Strategy

A pilot study presented by Omar Khan and colleagues, Wayne State University School of Medicine, Detroit, Michigan, suggested that glatiramer acetate 20 mg SC may be equally effective whether administered once daily or every other day in patients with RRMS. Among 30 patients randomized to the 2 dosage schedules, no differences in relapse rates, disease progression, change in T2-weighted lesion volume, or Gd-enhanced lesions were found at 2 years. Moreover, in vitro proliferation of glatiramer acetate-responsive T cells and Th1/Th2 cytokine expression did not differ between groups at any point. After 2 years, all patients in the once-daily treatment group switched to every-other-day treatment. At 4 years, no differences in the endpoints were found between the crossover group and the patients who had continuously received glatiramer acetate on an every-other-day basis. The researchers suggest that larger, multicenter trials are warranted to confirm these findings and to identify an optimal dosage for glatiramer acetate in RRMS.

Induction Therapy

Short-term induction therapy with mitoxantrone prior to treatment with glatiramer acetate resulted in substantial suppression of clinical disease activity in patients with active RRMS, according to a study by Jason Ramtahal and Mike Boggild, Walton Centre for Neurology and Neurosurgery, NHS Trust, Liverpool, United Kingdom. The study enrolled 77 patients, all of whom received mitoxantrone induction therapy: 58 received 48 mg/m² over 8 months and the others (earlier-treated patients) received somewhat higher total dosages. This mitoxantrone induction overlapped with glatiramer acetate therapy for the final 3 months, after which all patients received glatiramer acetate alone. The annualized relapse rate was reduced from 1.85 pre-induction to 0.16 or less at a mean follow-up of 44 months and was sustained up to 6 years.

Vaccination Approach

Heather B. Streeter and colleagues, University of Bristol, United Kingdom, described data showing that ATX-MS1467, a peptide vaccine for MS, was safe and well tolerated in a study of 6 patients with SPMS. After receiving escalating doses of ATX-MS1467 (25 to 800 mg), these patients exhibited no treatment-related or serious adverse events. In 4 patients who had a significant T-cell response to myelin basic protein before the trial, this response was significantly suppressed at 1 month after the administration of ATX-MS1467 ($P=0.0313$).

Proof-of-Concept Study for Antisense Oligonucleotide

Antisense oligonucleotides bind to and inhibit specific mRNA sequences. ATL1102 is an antisense inhibitor of

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VLA-4 mRNA, thereby inhibiting activated T-cell adhesion to endothelial cells, preventing their migration into the central nervous system. A proof-of-concept study demonstrated that 8 weeks of treatment with ATL1102 significantly reduced the cumulative

number of new active lesions in patients with RRMS. The results were reported by Volker Limmroth, University of Cologne, Cologne, Germany, and colleagues. Among 74 patients, those randomized to ATL1102 200 mg SC twice weekly had

a 54.4% decrease in the cumulative number of new active lesions when compared with the placebo group ($P=0.01$). Treatment with ATL1102 also reduced the cumulative number of new T1 Gd-enhanced lesions by 66.7% ($P=0.002$). ■

From CIS to Clinically Definite MS

Recent studies of early treatment in patients with CIS have shed light on the utility of MRI prognostic indicators, as well as the impact of disease-modifying therapy, on conversion to clinically definite MS.

Five-year results from the Betaferon® in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study contributed additional evidence supporting the efficacy of early treatment with IFN β -1b in patients with a first event suggestive of MS. According to Mark S. Freedman, Ottawa Hospital, Ottawa, Ontario, Canada, and colleagues, 358 of the original 468 patients enrolled in BENEFIT were followed for 5 years. Of these patients, 292 had originally been randomized to IFN β -1b and 176 to placebo for 2 years or until the development of CDMS. After that point, all patients were offered the opportunity to take IFN β -1b. Consistent with the results of an analysis at 3 years of follow-up, the 5-year data showed that early treatment with IFN β -1b, as opposed to delayed treatment, significantly reduced the risk of developing CDMS (by 37%; $P=0.003$). Early therapy also led to a significant decrease in relapse rate (by 20%; $P=0.015$), as well as a significant reduction in the formation of new lesions. The 3-year analysis had found that the risk of confirmed progression (according to the EDSS) fell by 40% ($P=0.0218$) with early treatment vs delayed treatment. At 5 years, a 24% reduction was identified but was

not statistically significant. However, the investigators found that quality of life remained high and was stable over time in both groups, although the early treatment group performed significantly better than the delayed treatment group on the Paced Auditory Serial Addition Task for cognitive function at both 3 ($P=0.0106$) and 5 ($P=0.004$) years.

Another analysis from the BENEFIT study showed that early treatment with IFN β -1b was unlikely to affect the usefulness of baseline MRI variables for predicting conversion to clinically definite MS in patients with CIS. As described by Bastiaan Moraal, VU University Medical Center, Amsterdam, The Netherlands, and colleagues, the analysis was based on 3-year data from 468 patients enrolled in BENEFIT who had a first demyelinating event and received either early treatment with IFN β -1b or delayed treatment (placebo followed by IFN β -1b after conversion to clinically definite MS or after 2 years of follow-up). The overall rate of conversion to CDMS was 42%. The greatest prognostic value was apparent with findings of ≥ 9 T2 lesions (hazard ratio 1.64; 95% confidence interval 1.15–2.33) and ≥ 3 periventricular lesions (hazard ratio 1.66; 95% confidence interval 1.14–2.41). The conversion rate increased with the cumulative number of positive criteria, and there was no specific advantage for using a fixed cutoff point of ≥ 3 Barkhof criteria.

The prognostic value was not affected by treatment in cases of clinically definite MS. For MS according to McDonald criteria, the overall rate of conversion was 78% and all MRI criteria exhibited predictive value (hazard ratio ranging from 1.38 to 2.72). On the other hand, treatment significantly affected the prognostic value of the presence of 4 positive Barkhof criteria ($P=0.002$).

The efficacy of early treatment with glatiramer acetate in patients with CIS was reported by Maria A. Rocca, Scientific Institute and University Ospedale San Raffaele, Milan, Italy, and colleagues, for the PreCISe Study Group. The study enrolled 481 patients who were randomized to receive either glatiramer acetate or placebo soon after the first clinical event suggestive of MS. Over 3 years of follow-up, the risk of developing clinically definite MS was reduced significantly (by 45%) with glatiramer acetate compared with placebo (hazard ratio for time to conversion to clinically definite MS 0.55; $P=0.0005$). Glatiramer acetate was also associated with a significant 58% decrease in the number of new T2-weighted lesions ($P<0.0001$) and a significant decrease in exposure-adjusted T2-weighted lesion volume ($P=0.0002$). Furthermore, the numbers of new T1 Gd-enhanced lesions and new T1 hypointense lesions were significantly reduced in the glatiramer acetate group vs the placebo group ($P=0.0001$ for both comparisons). ■

Results From Long-Term Clinical Trial Data

Long-term follow-up data from MS clinical trials are contributing to a greater understanding of the effects of disease-modifying therapy over time. New MRI data have also been shown to be predictors of long-term outcome in patients with MS.

Open-Label Studies

A 15-year follow-up of the ongoing, open-label US glatiramer acetate trial confirmed the benefits of long-term therapy with this agent. Corey Ford, University of New Mexico School of Medicine, Albuquerque, New Mexico, and colleagues noted that a mITT analysis included all patients who received at least 1 dose of glatiramer acetate (n=232). *[Editor's disclosure: Dr. Ford is a Neura editorial board member and an editor of this issue of Neura Special Report.]*

Another analysis focused on 100 patients who had continued in the study as of February 2008. The mean duration of treatment in these 2 groups was 8.6 and 13.6 years, respectively.

Relapse rates in the mITT cohort decreased from 1.18 to 0.43 per year. A total of 32% of patients had progression of disease, whereas 54% had stable or improved scores on the EDSS.

In the cohort of patients receiving ongoing therapy, the relapse rate fell from 1.12 to 0.25 per year.

A total of 38% of patients had disease progression, and 57% were either stable or improved. The time for 1 quartile of patients to reach an EDSS score of 4 was 3.98 years in the mITT cohort and 6.8 years in the ongoing cohort.

The data also showed that 75% of the mITT patients with a mean disease duration of 17 years and 65% of the ongoing cohort with a mean disease

duration of 22 years did not reach SPMS by the 15th year while on glatiramer acetate.

Patients in the open-label ASSURANCE trial of IM IFN β -1a were assessed for 15-year outcomes. The results were presented by Robert A. Bermel, Cleveland Clinic Foundation, Cleveland, Ohio, and colleagues. Data were available from 103 patients, 53

Changes in brain parenchymal fraction and whole-brain magnetization transfer ratio showed better correlation with clinical status than conventional MRI techniques.

(51%) of whom had received IM IFN β -1a for up to 17.3 years at the time of the follow-up analysis. The median duration of treatment was 13.3 years in long-term users and 6.0 years in non-long-term users. Significantly fewer long-term users than non-long-term users reached an EDSS score of 6.0 (30% vs 60%, respectively; $P=0.002$).

Predictors of Disability

Nancy D. Richert, National Institutes of Health, Bethesda, Maryland, and colleagues reported that MRI measures of tissue damage were stronger predictors of clinical disability than conventional MRI measures in patients with RRMS. These conclusions came from a retrospective study of 28 patients with RRMS and 3 with SPMS who were treatment naïve at baseline.

Of these patients, 70% received

standard disease-modifying therapy and 30% remained untreated. During the next 5 years, 17 patients remained clinically stable whereas 14 had a 2-point worsening in EDSS score (from a score of 1.5 at baseline to 3.75 at 5 years; $P=0.01$).

Conventional MRI measures at baseline (such as Gd-enhanced lesions or T2 lesion load) did not differ between these groups. However, both the brain parenchymal fraction at baseline and the change in brain parenchymal fraction over 5 years correlated with worsening of the patients' clinical status ($P=0.05$ and $P=0.003$, respectively). In addition, the change in whole-brain magnetization transfer ratio over 5 years was significantly predictive of clinical worsening ($P=0.006$).

Sustained progression on the EDSS is a useful predictor of long-term disability in patients with RRMS. Richard Rudick, Cleveland Clinic Foundation, Cleveland, Ohio, and colleagues made this observation after conducting post-hoc analyses of data from the pivotal phase 3 study of IM IFN β -1a in this population.

A total of 160 patients were included in an 8-year analysis and 116 patients in a preliminary 15-year analysis. Patients with EDSS progression over 2 years were significantly more likely to reach all EDSS milestones (scores $\geq 4, 5, 6, \text{ or } 7$) at 8 years or 15 years (all $P \leq 0.001$). These EDSS score milestones are widely recognized as correlating with permanent neurologic disability.

Compared with placebo, IM IFN β -1a significantly reduced the likelihood of reaching EDSS scores of 4 or 5 at 8 years ($P=0.007$ and $P=0.01$, respectively). T2 lesion volume also correlated significantly with reaching all EDSS milestones at 8 years (all $P < 0.05$). ■

Pediatric MS Risk Factors & Disease Characteristics

Several reports at the 2008 WCTRIMS meeting offered new insights into the pathophysiology and other characteristics of MS in children.

Vitamin D Insufficiency

Vitamin D insufficiency appears to be a risk factor for acquired demyelination in children and may contribute to earlier development of MS, according to a study presented by Heather E. Hanwell, University of Toronto, Ontario, Canada, and colleagues. They evaluated serum concentrations of 25-hydroxyvitamin D (25[OH]D) at the time of initial central nervous system demyelination in 125 children. *[Editor's note: 25(OH)D, or calcidiol, assay is the most accurate clinical measure for serum concentration of vitamin D; 25(OH)D is derived from cholecalciferol D₃, which is natural vitamin D, and is converted in the kidney to 1,25-dihydroxy vitamin D₃, the active molecule.]* Data from a 1-year follow up showed that 20 patients (16%) were diagnosed with MS an average of 222±209 days after collection of the baseline serum sample. Vitamin D insufficiency (defined as serum 25[OH]D ≤70 nmol/L) was identified in 68% of the overall study population. The mean serum 25(OH)D level was significantly lower in children who were ultimately diagnosed with MS than in those who did not experience additional clinical demyelinating events (47.6±20.6 nmol/L vs 60.2±28.9 nmol/L; $P=0.029$).

Atrophy as Predictor of CIS

Changes in brain volume can predict the risk of progression to MS in children with CIS. The study was reported by Paul S. Giacomini, Montreal Neurological Institute, Montreal, Quebec, Canada, and colleagues. This prediction of disease progression came from analy-

ses of serial MRI studies in 22 children with CIS. A total of 13 patients were classified as being at low risk for MS by virtue of remaining free from clinical relapse or MRI evidence of new lesions 12 months after the baseline scan. The other 9 children were considered to be at high risk because they had new lesions on subsequent MRI scans or were diagnosed with definite MS on the basis of clinical relapses.

Differences in brain volume changes were apparent between the 2 groups after 9 months of follow-up. Atrophy was evident in the high-risk group, which had a mean brain volume change of $-1.5\pm1.2\%$. In contrast, brain growth was observed in the low-risk group, which had a mean volume change of $0.3\pm1.1\%$. This difference was statistically significant ($P=0.002$). The investigators commented that these findings suggest both predictive and primary roles for neurodegeneration early in the disease process of MS. Furthermore, the observations raise concerns regarding the potential impact of brain atrophy on long-term physical and cognitive outcomes in affected children.

Disease Burden at Onset

A study described by Emmanuelle Waubant and colleagues, University of California San Francisco, San Francisco, California, demonstrated that the disease burden is higher and posterior cranial fossa involvement more common at the time of MS onset in children than in adults. Initial brain scans from 31 pediatric-onset and 31 adult-onset cases of MS were evaluated for lesions that were T2-bright, ovoid and well defined, large (>1 cm), or Gd enhanced. The median number of T2 lesions was significantly higher in children than in adults (21 vs 6; $P<0.0001$), as was the median number of large T2-bright areas (5 vs 1, respectively; $P<0.0001$). In addition, the

children had a significantly higher frequency of T2-bright foci in the posterior cranial fossa (74% vs 48% in adults; $P=0.037$) and were significantly more likely to have Gd-enhanced lesions (70% vs 25%, respectively; $P=0.0008$).

EBV & Risk of CIS

An evaluation of the seroprevalence of 5 common viruses among Canadian children presenting with CIS found that only remote [ie, not recent] infection with EBV was potentially associated with early diagnosis of MS. The study was reported by Brenda Banwell, Hospital for Sick Children, Toronto, Ontario, Canada, and colleagues.

Of 90 children (mean age 9.97 years), 51 (57%) were seropositive for remote EBV exposure, 32 (36%) for cytomegalovirus, 30 (33%) for parvovirus B19, 20 (22%) for herpes simplex viruses, and 77 (86%) for varicella zoster virus. Among 17 children (19%) who fulfilled the criteria for a diagnosis of MS at the time of this analysis, 75% were seropositive for remote EBV infection. This proportion did not differ significantly from that in the 73 children not yet diagnosed with MS (52%; $P=0.5$ corrected for age).

EBV nuclear antigen titers were higher in children with confirmed MS than in those with CIS, but the difference was not significant. The rate of seropositivity for EBV increased significantly with age (odds ratio 1.17; $P<0.001$). The likelihood of remote EBV infection did not vary by clinical presentation when adjusted for age, although monolesional presentations were significantly more common than polylesional presentations ($P=0.03$) or ADEM ($P<0.001$) among EBV-positive patients. EBV seronegativity was identified in 31 children, including 4 diagnosed with MS (23.5%), indicating that exposure to the virus is not a requisite factor for development of the disease. ■

Predicting MS Outcomes: Severity Scales, Genes, & Clinical Features

The ability to predict clinical outcomes among patients with MS is advancing in the wake of studies demonstrating the value of objective scales and monitoring strategies.

Superiority of the MS Severity Scale

The newly introduced MS Severity Scale was found to have better sensitivity for predicting disease progression as than EDSS score alone in a study by Joseph Herbert, New York University Hospital for Joint Diseases, New York, New York. The MS Severity Scale encompasses measurements of both disability (as assessed by the EDSS) and duration of disease. In this investigation, 251 patients with RRMS were randomized to receive glatiramer acetate 20 mg/day or placebo and were then followed for approximately 35 months. At baseline, MS Severity Scale scores were evenly distributed between the 2 treatment groups. Upon completion of the study, the median change in MS Severity Scale score from baseline was significantly greater in the group treated with glatiramer acetate as opposed to placebo (-0.73 vs -0.19 , respectively; $P=0.0019$). More patients in the glatiramer acetate group, compared with the placebo group, shifted to a lower severity level and fewer shifted to a higher severity level ($P\leq 0.0014$ for both). These data support the value of the MS Severity Scale as an effective tool for measuring disease progression, as it can take into account not only disability but disability in the context of the duration of the disease.

Demographic Predictors of Early Disease Course

Among patients eventually diagnosed with MS, those who are younger or of

non-white race/ethnicity have more severe and frequent initial demyelinating events, reported Emmanuelle Waubant, University of California San Francisco, San Francisco, California. Dr. Waubant and coworkers reached this conclusion after scoring the anatomic locations, severity, and recovery from first, second, and third demyelinating events in patients evaluated within the first year following the onset of MS. Less severe demyelinating event severity was found to predict recovery from a first or second demyelinating event. In addition, a severe initial event predicted a more severe second event (odds ratio 5.66; 95% confidence interval 2.38–13.49; $P<0.0001$), as well as third event (odds ratio 7.56; 95% confidence interval 1.87–31.27; $P=0.0046$). Correspondingly, a poor recovery from an initial event predicted poorer recovery from a second event (odds ratio 7.58; 95% confidence interval 2.74–20.98; $P<0.0001$) or third event (odds ratio 11.07; 95% confidence interval 1.64–74.51; $P=0.0135$). Moreover, non-white race/ethnicity and younger age were associated with an increased risk of relapse during the first year following disease onset. The hazard ratio for relapse was 2.39 among non-white patients (95% confidence interval 1.58–3.60; $P<0.0001$) and 1.51 for each 10-year decrease in age (95% confidence intervals 1.28–1.80; $P<0.0001$). Dr. Waubant commented that the question of whether genetic or biological factors are responsible for these patterns remains unanswered.

Predictive Utility of Genes

Research into the genetic underpinnings of MS has indicated that the HLA-DRB1*01 allele attenuates long-

term progression of disability. Previous findings have implicated this allele in disease resistance. To build on these observations, a study presented by George Ebers, University of Oxford, Oxford, United Kingdom, analyzed the role of the HLA-DRB1 locus on MS disease severity in 163 cases representing the extremes of distribution of long-term outcomes. Genotyping revealed that HLA-DRB1*01 was significantly underrepresented in malignant vs benign cases of disease. This finding was then replicated in a population of patients from Sardinia who had malignant or benign disease and in a cohort of affected sibling pairs who were discordant for HLA-DRB1*01. In the latter group, indices of mean disability progression were significantly lower among those with the HLA-DRB1*01 allele than in disease-concordant siblings who did not carry this allele. Dr. Ebers speculated that the protective effect of HLA-DRB1*01 in sibling pairs may be due to a specific epistatic interaction with the susceptibility allele HLA-DRB1*1501. On examination of high-density single nucleotide polymorphisms of the major histocompatibility index, no variants were found to differ between groups, suggesting that HLA-DRB1 may itself be the disease-modifying locus. Taken together, these results imply that HLA-DRB1*01 acts as an independent modifier of disease progression. Furthermore, these findings link susceptibility to long-term outcome. This suggests, Dr. Ebers commented, that shared quantitative major histocompatibility complex mechanisms are common to both susceptibility and long-term outcome, thus emphasizing the central role of the major histocompatibility complex region in MS pathogenesis. ■

**SPECIAL
REPORT**

Neura

*Highlights From the World Congress on
Treatment and Research in Multiple Sclerosis*

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Editors

COREY C. FORD, MD, PHD
University of New Mexico
Health Sciences Center
Albuquerque, New Mexico

STEPHEN S. KIRZINGER, MD
University of Louisville Medical School
Louisville, Kentucky

Over 5,000 multiple sclerosis experts, clinicians, and researchers gathered in Montreal for 4 days for the World Congress on Treatment and Research in Multiple Sclerosis, the first collaborative meeting between 3 major international multiple sclerosis organizations: the Americas Committee for Treatment and Research in Multiple Sclerosis, the European Committee for Treatment and Research in Multiple Sclerosis, and the Latin American Committee for Treatment and Research in Multiple Sclerosis. *Neura Special Reports* is pleased to bring you this coverage, devoted exclusively to the field of and developments in multiple sclerosis.

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