Meeting Highlights

Multiple Sclerosis Symposium and American Society of Hypertension

Walter Alexander

**MULTIPLE SCLEROSIS SYMPOSIUM**

Long-term efficacy data for glatiramer acetate (Copaxone, Teva Pharmaceuticals), which is indicated for patients with multiple sclerosis (MS), constituted a centerpiece among two days of presentations at the Fifth Teva and Sanofi-Aventis International Symposium on MS. Several hundred interested professionals attended the meeting, which took place from May 12–14, in Tenerife, Spain.

**Reduced Disability with Glatiramer: Results of a Long-Term Study**

Prevailing opinion suggests that the most effective options currently available for treating MS include the immunomodulatory therapy glatiramer acetate (GA) and the beta interferons, all of which were approved based on successful two-year pivotal trials.

Corey C. Ford, MD, PhD, Associate Professor of Neurology at the University of New Mexico in Albuquerque, said that although MS is a lifelong disease, the pivotal trials tell patients and physicians little about long-term control of symptoms and the likelihood of disease progression. Most studies of beta interferons are based on retrospectively gathered data with large gaps in monitoring, but only GA has been examined in a systematic, prospectively designed, long-term study of its use for more than a decade.

The ongoing U.S. Glatiramer Acetate (U.S. GA) Trial is now in its 15th year. Among the unique aspects of this trial are its in-clinic evaluations of patients to assess disability every six months and the fact that patients have been receiving GA monotherapy. No prospective studies of continuous interferon use go beyond four years, Dr. Ford said. Furthermore, patients who had withdrawn from the U.S. GA study (because they discontinued GA therapy for any reason) were sought for long-term follow-up clinical neurological assessment, as measured by the Expanded Disability Status Scale (EDSS).

As of this writing, 108 patients are receiving GA, out of an initial cohort of 232 patients who received at least one GA dose. Of the 124 patients who have withdrawn from the study, 50 have been followed over the long term.

The objective of the U.S. GA Study was to determine the efficacy and safety of GA treatment for up to 12 years among patients who had received at least one GA dose during the 30-month double-blind phase (the pivotal trial) or during the ongoing open-label extension study. Another purpose was to gather data about patients who had withdrawn from the study.

The first analysis covered the annual rate of relapse. The mean annual relapse rate, before GA therapy was initiated, was about 1.2%. For patients who continued to take GA, the relapse rate declined within a few years, to about 0.25% per year. The relapse rates during years 9 to 12 were even somewhat lower.

An analysis of the proportion of patients reaching EDSS thresholds of 4 (moderate disability), 6 (cane needed), or 8 (wheelchair needed) showed significantly reduced disability in the patients in the ongoing study compared with those who had withdrawn from the study (Table 1). The mean change was a loss of one-half step for patients continuing GA therapy and a loss of 2.24 steps, as assessed by the EDSS, for patients who had withdrawn, at a mean of about 4.3 years.

The proportion of patients remaining clinically stable or improved (with an EDSS increase of 0.5 points or less) while continuing GA therapy was 58% in the modified intent-to-treat group (the original cohort minus patients who had originally been given placebo and who never received a GA dose), 62% in the ongoing therapy group, and 56% in the withdrawal group. That same “clinically stable or improved” EDSS measure at the 10-year follow-up visit revealed a rate of 62% for the ongoing therapy patients and 28% for the patients who had withdrawn from the study.

“Roughly two thirds are staying stable or improved over the long term,” Dr. Ford said.

He emphasized that the long-term GA EDSS scores compared favorably with those from natural history reports. For example, the 15-year report by Weinschenker showed 50% of patients reaching an EDSS threshold of 6; and the Pittco 10-year report showed that 28% of patients did. The rates in the U.S. GA Study were 8% for ongoing patients and 50% for those who withdrew.

Dr. Ford noted that with a disease duration of about 15 years, nearly all patients receiving GA (89%) remained ambulatory and that 47% of patients who had ever received GA remained in the study and continued daily therapy.

<table>
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<tr>
<th>Table 1 Patients Receiving Ongoing Glatiramer Therapy versus Withdrawn Patients at 10 Years of Long-Term Follow-up</th>
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<tbody>
<tr>
<td>EDSS Measure</td>
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<tr>
<td>EDSS score of 4 (moderate disability)</td>
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<td>EDSS score of 6 (cane needed)</td>
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<td>EDSS score of 8 (wheelchair needed)</td>
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EDSS = Expanded Disability Status Scale.
He concluded that glatiramer provided reduced relapse rates and slowed the progression of disability over 10 years of continuous use in relapsing–remitting MS. However, he cautioned that we cannot be sure that the 50 patients who withdrew and who were followed are representative of the total cohort; similarly, we cannot be sure that the ongoing patients are completely representative of the natural history of MS.

“We can argue about that,” he said.

References

AMERICAN SOCIETY OF HYPERTENSION

**Aliskiren (Rasilez, Novartis), a direct renin inhibitor and the first in a new class of antihypertensive drugs to be introduced in a decade, has been submitted for approval by the Food and Drug Administration (FDA).** In clinical trials presented at the American Society of Hypertension’s Annual Scientific Meeting and Exposition (ASH 2006), aliskiren provided uninterrupted blood pressure (BP) control over 24 hours in combination with hydrochlorothiazide (HCTZ), a diuretic. This year’s meeting took place from May 16 to May 20, 2006.

Valsartan (Diovan, Novartis) is an FDA-approved angiotensin II receptor blocker (ARB) known to reduce high sensitivity C-reactive protein (hsCRP) levels. A combination of valsartan and HCTZ also controlled BP but raised the specter of a possible inflammatory effect for HCTZ.

**Aliskiren with HCTZ**

Jerry Mitchell, MD, of the Texas Center for Drug Development in Houston, noted that variability in BP is associated with damage to the heart, kidney, brain, and other organs. The benefits of BP reduction are maximized if control is maintained continuously. Furthermore, he said, the continuity and smoothness of BP lowering with antihypertensive agents can be assessed via 24-hour ambulatory BP monitoring. Aliskiren’s half-life of about 40 hours allows for once-daily dosing.

In a substudy of the larger aliskiren trial, 833 patients were randomly assigned to receive one of three aliskiren doses (150 mg, 300 mg, 600 mg) or placebo. This substudy included 216 patients who had been evaluated before their first dose of aliskiren or placebo and at the end of eight weeks of treatment. Results showed that BP was effectively reduced with aliskiren (Table 2). BP lowering was consistent at all doses at each hourly point, including the high-risk early morning period, when dangerous surges in BP often occur. With the 300-mg dose of aliskiren, the trough-to-peak ratio of 0.98 reflected a nearly complete preservation of BP-lowering effect just before the next dose.

The trough-to-peak ratio was 0.64 with 150 mg of aliskiren and 0.86 with 600 mg. High smoothness indices for aliskiren, when compared with those for placebo, reflected a smaller degree of variability in 24-hour BP measurements.

The mean BP with placebo surged to hypertensive levels in the morning. Mean reductions in daytime and nighttime diastolic BP and systolic BP were similar in the aliskiren patients. “The drug very effectively eliminates morning surges,” Dr. Mitchell said, adding that the incidence of stroke rises by 25% to 30% for every surge of 10 mm Hg in morning BP.

He concluded, “Once-daily aliskiren has the potential to maximize end-organ protective benefits through continuous, smooth BP lowering.”

**Placebo and Aliskiren Monotherapy**

A further analysis by Alberto Villamil, MD, from Fundapres, Buenos Aires, Argentina, compared placebo and aliskiren alone (75–300 mg), HCTZ monotherapy (6.25–25 mg), and eight aliskiren/HCTZ dose combinations. In a trial of approximately 2,800 patients, both aliskiren and HCTZ produced significantly greater reductions in mean average diastolic and systolic BP compared with placebo.

Responder rates reached 80.6% with aliskiren 300 mg/HCTZ 12.25 mg and 45.8% with placebo (*P < .0001*). The responder rate for aliskiren monotherapy 300 mg was 63.9%, and the rate for HCTZ 12.25 mg alone was 60.6%. Overall, the treatments were well tolerated, and the incidence of adverse drug events (ADEs) was unrelated to the dose.

Dr. Villamil concluded that aliskiren monotherapy effectively lowered BP; in combination, it provided significant additional BP reductions and an increased proportion of responders.

**Valsartan**

A large-scale clinical trial comparing the ARB valsartan (Diovan) with the same ARB plus HCTZ revealed unexpected findings and raised new questions. The ARB/HCTZ combination lowered BP successfully but significantly increased the inflammatory marker hsCRP.

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<th>Table 2</th>
<th>Ambulatory Blood Pressure Monitoring: Mean 24-Hour Change from Baseline Values at Eight Weeks</th>
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<tr>
<td><strong>Placebo</strong></td>
<td><strong>Aliskiren 150 mg once daily</strong></td>
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<tr>
<td>Mean average diastolic (mm Hg)</td>
<td>+1.61</td>
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<tr>
<td>Mean average systolic (mm Hg)</td>
<td>+1.75*</td>
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*P < .001 versus placebo.*

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Professor Paul Ridker, MD, MPH, study author of the Val-MARC trial (Valsartan: Managing BP Aggressively and Evaluating Reductions in hsCRP) from Brigham and Women’s Hospital in Boston, had earlier shown that hsCRP interacts with elevated BP to increase cardiovascular risk, predicting incident hypertension, heart attacks, and strokes in normotensive individuals. Angiotensin II is also known to be a potent pro-inflammatory mediator, and ARBs have been reported to reduce hsCRP. However, he commented that biomarkers are a “difficult story,” particularly when it comes to “figuring out what is clinically useful.”

The stakes are substantial, he added, at a Novartis-supported symposium, “Prevention of Hypertension and Cardiovascular Disease,” and in an oral session at the ASH meeting. Patients with low low-density lipoprotein-cholesterol (LDL-C) levels but high CRP levels—a group representing about 25% of the U.S. population—are at higher cardiovascular risk than individuals with high LDL levels and low CRP levels. That “high CRP group,” he added, has become a focus for reducing BP and cardiovascular events.

The first major unknown: Is hsCRP a risk marker or a risk factor?

The objective of the randomized Val-MARC trial was to determine the answer to an essential but more preliminary question: Do the effects of ARBs on hsCRP concentrations result from systemic intravascular pressures, or are they independent of BP reductions?

In the trial, 1,668 patients with a BP of 160–185/100–109 mm Hg received valsartan 160 mg once daily (with a forced titration to 320 mg once daily) or the same valsartan dose plus HCTZ at 12.5 mg once daily (which could be doubled at week 12 at the physician’s discretion). The primary endpoint was a change in BP or hsCRP at week six.

At the sixth week, patients receiving valsartan plus HCTZ had mean reductions of 25 mm in Hg systolic BP and 14 mm Hg in diastolic BP that were significantly greater ($P < .001$) than patients receiving valsartan alone. For the valsartan-alone group, the average systolic BP was reduced by 18 mm Hg systolic and the average diastolic BP was reduced by 9 mm Hg.

Changes in hsCRP, however, diverged in the two groups: patients experienced a 9% reduction with valsartan monotherapy and an increase greater than 4% ($P < .001$) with ARB/HCTZ. The anti-inflammatory effects of valsartan were maintained at 12 weeks.

Dr. Ridker concluded that valsartan’s anti-inflammatory effects appeared to be independent of BP reductions and “may be neutralized by HCTZ.” He also stated:

“An aggressive strategy, utilizing combination therapy in patients with early stage 2 hypertension, resulted in substantially greater blood pressure reductions, potentially reducing atherosclerotic risk.”

The possibility of contradictory therapeutic implications is striking and raises another key question: Will the Val-MARC trial’s finding of lowered inflammation, independent of BP reduction with valsartan monotherapy, translate to net clinical advantages?

“That,” Dr. Ridker answered, “will require well-designed prospective trials.”