Simvastatin Trial Suggests That Statins May Treat PCOS

BY JANE SALODOF MACNEIL
Southwest Bureau

LOS ANGELES — Simvastatin lowered testosterone levels by 41%, normalized gonadotropin levels, and reduced cardiovascular risk factors in a small, randomized, controlled trial, suggesting that statins may be a potential treatment for polycystic ovary syndrome.

"Statins would improve the metabolic profile in those patients in terms of lipid levels as well as improve the hormonal problems," study investigator Antoni J. Duleba, M.D., said at the annual meeting of the Society for Gynecologic Investigation.

The study is the first to demonstrate these benefits in women with polycystic ovary syndrome (PCOS). Dyslipidemia is common with PCOS, but statins are almost never used in PCOS, because the patients are typically young women trying to get pregnant or are at risk of getting pregnant. Statins are contraindicated in pregnancy, said Dr. Duleba of Yale University, New Haven.

The study eliminated pregnancy as a consideration by placing all 48 study participants on oral contraceptive pills (OC) containing 20 mcg of ethinyl estradiol and 150 mcg of desogestrel. One 24-patient cohort was treated with 20 mg of simvastatin daily, along with OC; the other 24 patients received only OC.

Investigators from Yale and Poznan University of Medical Sciences in Poland are conducting the ongoing trial in that country. The women are about 23 years old on average. None received any hormonal treatment or OCs for at least 3 months before enrollment. Organon Inc. supplied the OC Marvelon, and Polfa, a Polish pharmaceutical company, provided simvastatin.

A comparison of hormonal levels at baseline and 12 weeks showed total testosterone fell significantly—an average of 34.6 ng/dL (41%) in the OC-simvastatin group. By contrast, in the OC-alone group, levels fell by only 10.9 ng/dL (14%).

Average dehydroepiandrosterone sulfate (DHEA-S) fell 26% in the OC-simvastatin patients and 28% in the OC-alone group. Luteinizing hormone (LH), however, was reduced 43% in the OC-simvastatin group vs. 9% in the OC-alone cohort.

FSH declined 8%, which was not significant, in the OC-simvastatin patients, but it increased 21% in those taking just OCs.

The LH:FSH ratio declined significantly in the OC-simvastatin group (44%) and fell by 12% in the OC-alone group—not a statistically significant decline.

As expected, the simvastatin group had a significantly improved metabolic profile: Total cholesterol was 10% lower with OC-simvastatin vs. 8% higher with OC alone. Low-density lipoprotein (LDL) cholesterol dropped a significant 24% in the OC-simvastatin patients, but stayed the same in the control group. Conversely, triglyceride levels increased 21% in the OC-only patients but were not much changed in OC-simvastatin patients.

Increases in HDL cholesterol levels were similar: 9% with OC-simvastatin and 13% with OC alone.

Neither group had a significant improvement in insulin sensitivity or change in body mass index.

Dr. Duleba reported that hyperandrogenia declined dramatically in the OC-simvastatin arm, but he said 3 months is too early to determine whether this will lead to improvements in excessive hair growth or other clinical conditions associated with PCOS.

The trial employs a crossover design by which the groups have since switched regimens. The investigators also are looking at biochemical markers of endothelial function and cardiovascular risk.

"We used to only see women who wanted to get pregnant and, on occasion, because of complaints of hirsutism," he said. "Now, with greater understanding of cardiovascular risk factors, people come to the office and say, 'What can we do to protect ourselves from heart disease, diabetes, high blood pressure—all the cardiovascular problems that our mothers, aunts, and grandmothers had?' "

Although he would not recommend statins to women trying to get pregnant, he concluded that statins could eventually prove to be the answer to their question about cardiovascular risk. ■

Metformin Reduces CV Risk in PCOS Patients

BY HEIDI SPLETE
Senior Writer

WASHINGTON — Metformin combined with a reduced-calorie diet reduced cardiovascular risk in a study of 791 women with polycystic ovary syndrome, Mofiz Haque, M.D., reported in a poster presented at the Clinical Research 2005 meeting.

The metformin-diet (MET-D) combination was effective in reducing weight, triglycerides, and LDL cholesterol, while increasing HDL cholesterol, reported Dr. Haque of the cholesterol center at the Jewish Hospital, Cincinnati, and his colleagues.

At baseline, the women had a median weight of 95 kg; 15% were overweight, 46% were obese, and 29% were severely obese. At baseline, the mean triglyceride level was 108 mg/dL, LDL cholesterol was 116 mg/dL, and HDL cholesterol was 46 mg/dL.

Women with a BMI less than 25 kg/m^2 were given a 2,000-calorie per day diet, and those with a BMI of 25 kg/m^2 or higher were given a 1,500-calorie diet. Each diet included 26% of calories from protein and 44% from carbohydrate, they noted at the meeting, sponsored by the American Federation for Medical Research.

Overall, metformin targeted to 2,500 mg/day in combination with dietary restriction was associated with significant reductions in weight, triglycerides, LDL cholesterol, and blood pressure.

The mean weight loss was 5 kg (5%), 6 kg (6%), and 5 kg (5%) for women who took medication for 12-18 months, 18-24 months, and more than 24 months, respectively. In those three groups, 13%, 14%, and 15% of the women lost at least 15% of their body weight.

Triglyceride levels dropped significantly—by 17 mg/dL—among the 65 women who followed the MET-D regimen for 18-24 months.

LDL cholesterol levels fell an average of 6 mg/dL (4%) and 9 mg/dL (7%), respectively, among the 102 women who followed the regimen for 12-18 months and the 210 women who followed the regimen for more than 24 months.

HDL cholesterol levels rose an average of 2 mg/dL (6%) and 4 mg/dL (8%) among women who followed the regimen for 18-24 months and more than 24 months, respectively. Both increases were statistically significant.

About 75% of women with polycystic ovary syndrome are obese, with unhealthy triglyceride and cholesterol levels. MET-D appears to be an effective strategy for helping them lose weight and reduce associated cardiovascular risk factors, they noted. ■

Switching Patients From Valproate May Reverse Hormonal PCOS

BY BRUCE JANCIN
Denver Bureau

BRECKENRIDGE, COLO. — Hormonal evidence of polycystic ovary syndrome in patients on valproate is often reversed by a switch to one of the newer antiepileptic drugs, Jacci Bainbridge, Pharm.D., reported at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

Women with epilepsy are known to have an increased frequency of polycystic ovary syndrome (PCOS), a common complication of valproate therapy. Evidence that the associated adverse neuroendocrine changes are reversible with a change in seizure medication comes from a recent study by investigators at the University of Birmingham (England), said Dr. Bainbridge of the University of Colorado, Denver.

At the annual meeting of the American Epilepsy Society, the British investigators reported on 16 women with generalized epilepsy who had been taking valproate for longer than 2 years. They ranged in age from 16 to 27 years, and nine had been diagnosed with juvenile myoclonic epilepsy. All 16 patients had the elevated testosterone and/or FSH levels that help define PCOS.

Patients were initially switched from valproate to lamotrigine (Lamictal). If their seizures worsened on the new medication, they were switched again, this time to levetiracetam (Keppra). Eleven women finished the study on lamotrigine.

All five patients who were switched to levetiracetam became seizure free. Of the 16 patients, 15 lost hormonal evidence of PCOS during the switch from valproate, she said.

Conference director Jose F. Cavazos, M.D., said that rather than doing routine hormone measurements in his valproate-treated patients in an effort to identify those with hyperandrogenism, he relies upon sudden weight gain as an early clinical tip-off to the presence of PCOS.

Weight gain in this setting is often due to the insulin resistance that is one of the first manifestations of PCOS.

There are some data to suggest that there is a dose-dependent relationship between the use of valproate and PCOS. It may be possible to use the drug at lower doses without increasing the risk of the hormonal/metabolic disorder. That's welcome news because valproate remains a useful drug in certain circumstances.

"Patients with refractory primary generalized epilepsy are going to end up on multiple medications—and one of them is often Depakote [valproate]," noted Dr. Cavazos of the University of Texas at San Antonio.

Seizures can entail hypothalamic storm, with resultant long-term adverse effects on the hypothalamic-pituitary-ovarian axis. One outcome can be premature ovarian failure, which is more common in women with epilepsy. This helps explain the relatively low birth rate among women with epilepsy, he said.

Dr. Cavazos mentioned one study in which investigators evaluated 50 consecutive women with epilepsy aged 38-64 years whose seizures began prior to age 41. A control group included 82 age-matched neurologically normal women. Of the women with epilepsy, 14% had onset of menopause prior to 42 years, compared with just 4% of controls (Epilepsia 2001;42:1584-9).

In another study, Cynthia L. Harden, M.D., of Columbia University, New York, demonstrated that seizure frequency and lifetime number of seizures were associated with earlier age at menopause, according to Dr. Cavazos.

She surveyed 68 women with epilepsy whose mean age at menopause was 47.8 years. The 15 women classified as having a low-seizure-frequency history had a mean age at menopause of 49.9 years, compared with 47.7 years in the intermediate-seizure-frequency group and 46.7 years in the 28 women with high seizure frequency. The age difference was statistically significant (Neurology 2003;61:451-5). ■