OBSTETRICS

Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial

Maged M. Costantine, MD; Kirsten Cleary, MD; Mary F. Hebert, PharmD, FCCP; Mahmoud S. Ahmed, PhD; Linda M. Brown, DrPH; Zhaoxia Ren, MD, PhD; Thomas R. Easterling, MD; David M. Haas, MD, MS; Laura S. Haneline, MD; Steve N. Caritis, MD; Raman Venkataramanan, PhD; Holly West, DHEd; Mary D'Alton, MD; Gary Hankins, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network

BACKGROUND: Preeclampsia complicates approximately 3—5% of pregnancies and remains a major cause of maternal and neonatal morbidity and mortality. It shares pathogenic similarities with adult cardiovascular disease as well as many risk factors. Pravastatin, a hydrophilic, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor, has been shown in preclinical studies to reverse various pathophysiological pathways associated with preeclampsia, providing biological plausibility for its use for preeclampsia prevention. However, human trials are lacking.

OBJECTIVE: As an initial step in evaluating the utility of pravastatin in preventing preeclampsia and after consultation with the US Food and Drug Administration, we undertook a pilot randomized controlled trial with the objective to determine pravastatin safety and pharmacokinetic parameters when used in pregnant women at high risk of preeclampsia.

STUDY DESIGN: We conducted a pilot, multicenter, double-blind, placebo-controlled, randomized trial of women with singleton, nonanomalous pregnancies at high risk for preeclampsia. Women between $12^{0/7}$ and $16^{6/7}$ weeks' gestation were assigned to daily pravastatin 10 mg or placebo orally until delivery. Primary outcomes were maternal-fetal safety and pharmacokinetic parameters of pravastatin during pregnancy. Secondary outcomes included rates of preeclampsia and preterm delivery, gestational age at delivery, birthweight, and maternal and cord blood lipid profile (clinicaltrials.gov identifier NCT01717586).

RESULTS: Ten women assigned to pravastatin and 10 to placebo completed the trial. There were no differences between the 2 groups in rates of study drug side effects, congenital anomalies, or other adverse or serious adverse events. There was no maternal, fetal, or neonatal death. Pravastatin renal clearance was significantly higher in pregnancy compared with postpartum. Four subjects in the placebo group developed preeclampsia compared with none in the pravastatin group. Although pravastatin reduced maternal cholesterol concentrations, umbilical cord cholesterol concentrations and infant birthweight were not different between the groups. The majority of umbilical cord and maternal pravastatin plasma concentrations at the time of delivery were below the lower limit of quantification of the assay. Pravastatin use was associated with a more favorable pregnancy angiogenic profile.

CONCLUSION: This study provides preliminary safety and pharmacokinetic data regarding the use of pravastatin for preventing preeclampsia in high-risk pregnant women. Although the data are preliminary, no identifiable safety risks were associated with pravastatin use in this cohort. This favorable risk-benefit analysis justifies using pravastatin in a larger clinical trial with dose escalation.

Key words: angiogenic, pharmacokinetics, pravastatin, preeclampsia, safety

Preeclampsia is a multisystem disorder that complicates 3-5% of pregnancies and remains a major cause of maternal, fetal, and neonatal morbidity and mortality.[1] It is characterized by angiogenic imbalance, exaggerated inflammation, and endothelial dysfunction, which ultimately lead to the clinical manifestations of hypertension, proteinuria, and end organ damage.[1,2]

Cite this article as: Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol 2016;214:720.e1-17.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.12.038

Preeclampsia is associated with serious short- and long-term maternal and neonatal morbidities,[1,3] and its recurrence in subsequent pregnancies depends on the presence of risk factors (eg, diabetes, hypertension, and multifetal gestation) and the severity and time of onset of preeclampsia in a prior pregnancy.[4,5]

Despite being unique to pregnancy, preeclampsia shares pathogenic similarities and many risk factors with adult cardiovascular disease.[4] Endothelial dysfunction and inflammation are fundamental for the initiation and progression of both atherosclerosis and preeclampsia.[2,6-8] Numerous attempts at primary and secondary prevention of preeclampsia, using various supplements and medications, have had limited success.[4] Only low-dose aspirin was found to have a modest benefit in reducing the rate of preeclampsia in an individual patient metaanalysis,[9] and that benefit was achieved only if the drug was started before 16 weeks' gestational age.

On the contrary, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase (statins) are effective in primary and secondary prevention of cardiovascular mortality and morbidity.[10,11] Moreover, statins have been used in animal models of preeclampsia to revert the angiogenic imbalance, a hallmark of preeclampsia, and restore endothelial dysfunction. This biological plausibility and data

from preclinical animal studies support a role for statins in preeclampsia prevention.[12-19]

Our long-term goal is to evaluate the utility of pravastatin (a hydrophilic statin) to reduce the recurrence of preeclampsia in high-risk pregnant women. As an initial step in this process, and after consultation with the US Food and Drug Administration (FDA), we undertook a pilot randomized controlled trial with an objective to evaluate the maternal-fetal safety and pharmacokinetic (PK) parameters of pravastatin when used in pregnant women at high risk for preeclampsia.[19] In this publication, we are reporting the first phase of a series of planned studies using a low dose (10 mg) of pravastatin.

Materials and Methods

Study population

We conducted a multicenter, double-blind, placebo-controlled randomized trial involving pregnant women at high risk for preeclampsia. Eligible women were 18 years old or older, with singleton, nonanomalous pregnancy between $12^{0/7}$ weeks and $16^{6/7}$ weeks' gestation (confirmed with an ultrasound examination), and with a history of severe preeclampsia in a prior pregnancy that required delivery prior to 34 weeks' gestation (documented by chart review).

We excluded women with known fetal genetic or major malformations; fetal demise; multifetal gestation; contraindications for statin therapy (eg, hypersensitivity to pravastatin, recent or active liver disease); concomitant therapy with fibrates, niacin, cyclosporine, clarithromycin, or erythromycin; pregestational diabetes mellitus; human immunodeficiency virus infection; history of solid organ transplant; chronic renal disease; epilepsy; uterine malformations; cancer; familial hypercholesterolemia; or inability to tolerate oral medications secondary to severe nausea and vomiting of pregnancy.

The trial was conducted from August 2012 through February 2014 by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Obstetric-Fetal Pharmacology Research Units Network at 5 clinical center sites as an FDA-approved investigational new drug study (IND; number 114205).[19] The institutional review boards at all the participating sites approved the study protocol. All women provided written informed consent. The study was registered on clinicaltrials.gov (identifier number NCT01717586).

Study design and intervention

Before randomization, all participants were documented to have normal liver transaminases (aminotransferase [AST] and aspartate aminotransferase [ALT]). Women were randomized to pravastatin 10 mg or placebo and were assigned a prepackaged supply of study medication corresponding to the appropriate study drug code. Randomization was performed through a central process that was prepared and maintained by the data coordinating center (RTI International, Research Triangle Park, NC).

Initial stratification was by clinical site. Pravastatin and placebo capsules were manufactured by University of Iowa Pharmaceuticals and packaged in identical capsules. Subjects were asked to take 1 capsule orally daily, and treatment continued until delivery or until a condition developed that required discontinuation of the study drug.

After randomization, research personnel followed up subjects at scheduled intervals. Subjects' care and that of their infants was according to standard practice. At each study visit, medication's side effects were assessed using a checklist, adverse events (AEs) were determined and assessed, and pill count performed. Subjects' pregnancy management (including antenatal testing, ultrasounds, management of preeclampsia, use of low dose aspirin, and others) was left to the discretion of the treating physician and performed as recommended by standard prenatal care as defined by the respective participating institution. All data were collected or abstracted by research coordinators at the clinical centers and uploaded to a central database that was managed by the data coordinating center, which was responsible for data analysis.

Pharmacokinetic studies

Steady-state pravastatin PK studies were conducted in the second trimester (18−24 weeks' gestation) and third trimester (30−34 weeks' gestation) of pregnancy as well as postpartum (4−6 months after the delivery). Each subject served as her own control.

Subjects recorded the time of pravastatin dosing for the 4 days prior to each study day, and pill counts were conducted to determine adherence. Women were asked to fast (except for water) for 5 hours prior to each study visit until 1 hour after dosing.

Serial blood samples (6 mL each) were collected for measurement of pravastatin and 3′α-isopravastatin (a major metabolite of pravastatin, that is only 1-10th to 1-40th as potent as parent drug in inhibiting HMG-CoA reductase) concentrations in plasma at times: before the dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after the dose on each pharmacokinetic study day.

Urine was collected before the dose, and then all urine over 1 dosing interval was collected as follows: 0−4, 4−8, 8−12, and 12−24 hours following the dosing on each study day. Urine from each interval was combined, mixed, and total volume measured. An aliquot from each interval was assayed for pravastatin and 3′α-isopravastatin concentrations.

Maternal, umbilical cord venous and umbilical cord arterial blood samples were collected at the time of delivery for measurement of pravastatin and 3′α-isopravastatin concentrations in plasma. All samples were stored at −70° C until analysis (more details on PK studies and analysis will be found in the supplemental materials).

Outcome variables

The primary outcomes were the maternal-fetal safety and the pravastatin PK parameters during pregnancy.

Safety outcomes included evaluation of medication side effects (checklist), maternal AEs, and serious AEs as well as fetal or perinatal death, and congenital malformations. Pravastatin PK parameters included maximum concentration (C_{max}) and time to