OBSTETRICS

Prospective, randomized, double-blind, placebo-controlled evaluation of the Pharmacokinetics, Safety and Efficacy of Recombinant Antithrombin Versus Placebo in Preterm Preeclampsia

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BACKGROUND: Despite expectant management, preeclampsia remote from term usually results in preterm delivery. Antithrombin, which displays antiinflammatory and anticoagulant properties, may have a therapeutic role in treating preterm preeclampsia, a disorder characterized by endothelial dysfunction, inflammation, and activation of the coagulation system.

OBJECTIVE: This randomized, placebo-controlled clinical trial aimed to evaluate whether intravenous recombinant human antithrombin could prolong gestation and therefore improve maternal and fetal outcomes.

STUDY DESIGN: We performed a double-blind, placebo-controlled trial at 23 hospitals. Women were eligible if they had a singleton pregnancy, early-onset or superimposed preeclampsia at 23 0/7 to 30 0/7 weeks' gestation, and planned expectant management. In addition to standard therapy, patients were randomized to receive either recombinant human antithrombin 250 mg loading dose followed by a continuous infusion of 2000 mg per 24 hours or an identical saline infusion until delivery. The primary outcome was days gained from randomization until delivery. The secondary outcome was composite neonatal morbidity score. A total of 120 women were randomized.

RESULTS: There was no difference in median gestational age at enrollment (27.3 weeks' gestation for the recombinant human antithrombin group [range, 23.1—30.0] and 27.6 weeks' gestation for the placebo group [range, 23.0—30.0]; P=.67). There were no differences in median increase in days gained (5.0 in the recombinant human antithrombin group [range, 0—75] and 6.0 for the placebo group [range, 0—85]; P=.95). There were no differences between groups in composite neonatal morbidity scores or in maternal complications. No safety issues related to recombinant human antithrombin were noted in this study, despite the achievement of supraphysiological antithrombin concentrations.

CONCLUSION: The administration of recombinant human antithrombin in preterm preeclampsia neither prolonged pregnancy nor improved neonatal or maternal outcomes.

Key words: anticoagulation, antiinflammatory, human, hypertension, phase III clinical trial, pregnancy, premature birth, prematurity

Preterm preeclampsia (PPE) at 23 to 30 weeks' gestation, although relatively rare in relation to the overall incidence of preeclampsia (PE), affects approximately 6000 to 8000 pregnancies per year in the United States and results in the delivery of high-risk and significantly premature neonates who experience a high rate of perinatal death and severe short- and long-term morbidities.[1–4] Expectant management is a recommended practice in selected patients with PPE and consists of careful medical surveillance of the mother and the fetus with the goal of extending pregnancy to decrease the prematurity complications.[5,6]

The current understanding of the PPE pathophysiology points to a number of derangements instigated by the placenta that affect the maternal endothelium and the kidney, including impaired vascular endothelial growth factor signaling, increased sensitivity to angiotensin II, endothelial dysfunction, and inflammation and activation of both the coagulation system and platelets.[7–9] The pleiotropic antiinflammatory and anticoagulant effects of antithrombin (AT) are hypothesized to have a therapeutic role in PE.[10–14] Nonclinical studies support the hypothesis and provide evidence of the efficacy of AT in preeclamptic animal models.[15,16] The evidence of benefit has been observed in preliminary trials demonstrating that plasma-derived AT prolonged gestational age (GA) and increased neonatal weight at birth.[17–21]

The prospective randomized, double-blind, placebo-controlled evaluation of the Pharmacokinetics, Safety and Efficacy of Recombinant Antithrombin Versus Placebo in Preterm Preeclampsia (PRESERVE-1) trial was designed to test the hypothesis that patients with PPE between 23 and 30 weeks' gestation randomized to receive recombinant

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AJOG at a Glance

Why was this study conducted?

This randomized, placebo-controlled clinical trial aimed to evaluate whether intravenous recombinant human antithrombin (rhAT) could prolong gestation and therefore improve maternal and fetal outcomes.

Key findings

Compared with placebo, the administration of rhAT in preterm preeclampsia neither prolonged pregnancy nor improved neonatal or maternal outcomes.

What does this add to what is known?

Antithrombin use did not lead to pregnancy prolongation or improvement in neonatal or maternal outcomes despite previous research suggesting that this intervention could be beneficial in the management of early-onset preeclampsia.

human antithrombin (rhAT) in addition to standard of care would demonstrate a longer interval from randomization to delivery (latency) than patients with PPE receiving placebo and standard of care.

Methods

Trial design and participants

We randomly assigned women aged at least 16 years with PPE and who were at 23 0/7 to 30 0/7 weeks' gestation with a singleton fetus to receive either rhAT or placebo. The primary efficacy endpoint was the difference in GA from the time of randomization into the study to delivery between rhAT-treated and placebo-treated women. Only subjects with PPE who were admitted to the hospital and had a period of evaluation and stabilization, ideally <48 hours from hospitalization, were considered for this study (Figure). This trial targeted early PPE, diagnosed between 23 and 30 weeks' gestation, given the significant perinatal morbidity and mortality associated with prematurity. We chose weekly cutoffs because we believed these would be the most clinically relevant time periods. We sought and received institutional review board approval from 26 participating centers. Exclusion criteria are presented in Supplemental Box.

Randomization and study-group assignments

Eligible women were randomly assigned in a 1:1 ratio to either rhAT or placebo. Randomization was blocked by study site using variable block sizes of 2 and 4. Throughout the trial, the randomization scheme was generated by Medidata (New York City, NY). Only unblinded Medidata staff, selected contract research organization, sponsor team, and pharmacy staff at each site had access to the randomization scheme. Women and investigators were blinded to treatment assignment. Unblinded pharmacy staff prepared the study drug. The definitions of PE and superimposed PE are presented in the Box.

Selection of recombinant human antithrombin dosing for the trial

Mean baseline levels in previous prospective or interventional studies of AT in PE were just below normal or low normal (60%−82%).[18−22] The effect of several rhAT treatment scenarios on the AT activity in pregnant women with PPE was simulated using population pharmacokinetic modeling. Predicted cumulative AT activities were compared with those reported for the treatment with plasma-derived AT in PPE.[18,21] The dose of rhAT was targeted to the same concentrations from plasma AT after bolus administration that yielded an efficacy signal in the Maki trial.[18] These target concentrations were determined through a pharmacokinetic model of plasma AT.

The trial drug (either rhAT or placebo) was administered through a dedicated intravenous line. Subjects randomized to rhAT received an initial loading dose of 250 mg rhAT for 15 minutes, immediately followed by a continuous infusion of 2000 mg rhAT per 24 hours for the duration of treatment. The total daily dose was 2250 mg on the first day of treatment and 2000 mg on subsequent days. Subjects randomized to placebo received an identical administration of normal saline. Continuous infusion dosing was planned to continue until a decision to deliver or the woman reached a GA of 34 0/7 weeks.

Follow-up visits

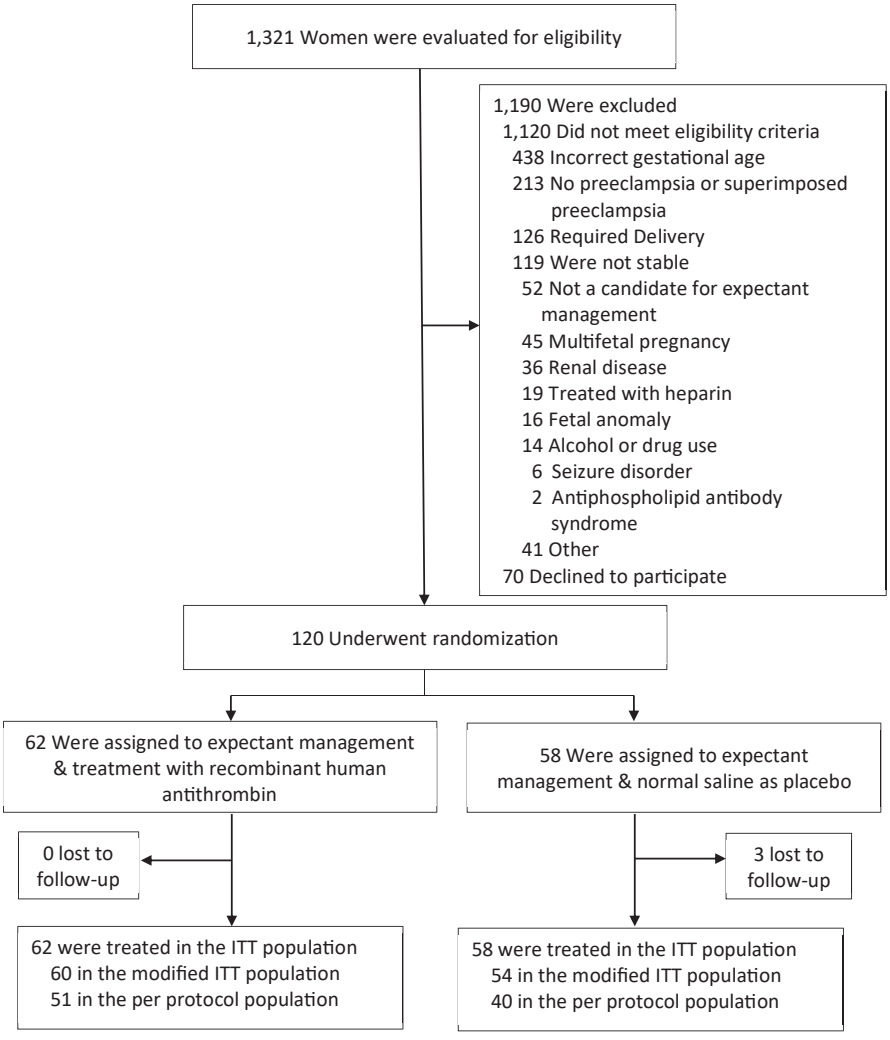
Posttreatment assessments of the mother were performed at hospital discharge and approximately 4 to 6 weeks after delivery. Information on the neonates was collected when they reached a postmenstrual age of 36 weeks. If the neonate reached 36 weeks' postmenstrual age at <28 days after delivery, the final neonatal follow-up was done at the 4- to 6-week postdelivery visit.

Outcome measures

The primary outcome was gestational days gained, which was defined as the GA at delivery minus the GA at randomization. The secondary outcome was a 5-point composite score based on specific fetal or neonatal adverse outcomes associated with prematurity (Supplemental Table 1). Neonatal outcomes of specific interest were assessed from birth to the 36 weeks' postmenstrual age and the 36 weeks' postmenstrual age visit or to the 4 to 6 weeks' postdelivery visit (if both the 36 weeks' postmenstrual age and the 36 weeks' postmenstrual age visit occurred <28 days after delivery). Maternal outcomes of specific interest are presented in Supplemental Table 2.

All investigators and their corresponding participating centers were skilled in the evaluation and management of PPE and agreed to follow the accepted Society for Maternal-Fetal Medicine and American College of Obstetricians and Gynecologists (ACOG) published guidelines for delivery. Several of the centers were also part of the Maternal-Fetal Medicine Units Network. Similarly, the neonatal intensive care units (NICUs) of the participating centers were part of the national NICU

FIGURE
Eligibility, randomization, and assessment



Patients were randomized at a 1:1 ratio with recombinant antithrombin as a 250 mg loading dose followed by continuous infusion at 2000 mg per 24 hours, or an identical saline infusion. Efficacy endpoints and outcomes were based on the ITT population: all women randomized according to their treatment assignment. Modified ITT population refers to all women in the ITT population who received study treatment. Per-protocol population refers to all women in the ITT population with no major protocol deviations.

AT, antithrombin; *ITT*, intent to treat.

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networks, which followed commonly accepted disease definitions and practice guidelines.

Adverse events

Safety assessments were performed throughout the treatment and follow-up periods.

Statistical analysis

The Shapiro-Wilk test was used to determine whether the data were normally distributed. An analysis of covariance was used to test for a difference in treatment effects between rhAT and placebo, in terms of treatment, type of PE (PE vs superimposed PE), and GA at study randomization (measured in days as a continuous variable). Continuous variables were summarized using descriptive statistics. Categorical data were summarized by frequencies and percentages. For dichotomous outcomes, odds ratios were estimated based on logistic regression models in terms of treatment, type of PE (PE vs superimposed PE), and GA at randomization. The sample size estimation was based on the results of the study by Maki et al.[18] We estimated that 34 women per study group would provide a power of 90% to detect a relative increase of 33% in the duration of the primary outcome, that is, days gained in GA, from 7.4 days in the placebo group to 9.7 days in the rhAT group. We increased the sample size to

BOX
Definition of preeclampsia and superimposed preeclampsia

Preeclampsia was defined as:

- Gestational hypertension defined as a recorded SBP of ≥140 mm Hg or DBP of ≥90 mm Hg on 2 occasions at least 4 h apart (since the commencement of medical intervention in any facility)

Or

- Severe gestational hypertension defined as SBP of ≥160 mm Hg or DBP of ≥110 mm Hg, confirmed with a second assessment within a short interval (min)

And new onset of any of the following:

- Proteinuria defined as ≥0.3 g protein per 24 h in a 12–24 h urine collection or PCR of ≥0.3 mg/mg (on a random sample or any collection period)
- Platelet count of <100,000/μL
- Serum creatinine concentrations of >1.1 mg/dL in the absence of other renal diseases
- Elevated liver transaminases to ≥twice the upper limit of normal
- Cerebral or visual symptoms

Superimposed preeclampsia was defined as:

- The start of antihypertensive medication, increasing the dose of a currently administered antihypertensive medication or adding a second antihypertensive medication after 20 wk of pregnancy for SBP of ≥160 mm Hg or DBP of ≥105 mm Hg in a subject who had a history of controlled hypertension before 20 wk of pregnancy

And new onset of any of the following:

- Proteinuria defined as ≥0.3 g protein per 24 h in a 12–24 h urine collection or PCR ratio of ≥0.3 mg/mg (on a random sample or any collection period)
- Platelet count of <100,000/μL
- Serum creatinine concentrations of >1.1 mg/dL in the absence of other renal diseases
- Elevated liver transaminases to ≥twice the upper limit of normal
- Cerebral or visual symptoms

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60 women per study group to assess safety, and we also employed an adaptive study design to better address the secondary outcome, that is, the 5-point composite score based on specific fetal or neonatal outcomes, given that contemporary robust data exist for prematurity, but not specifically for PPE.[23] An interim analysis was performed when primary efficacy endpoint data were available for the first 60 enrolled subjects (50%).

Results

Characteristics of the participants

From July 2014 to May 2016, 1321 women were screened and a total of 120 women were randomized to receive either rhAT (62 women) or placebo (58 women). Demographic and baseline clinical characteristics were similar between the 2 treatment groups (Table 1).

Delivery information

The indications for delivery, mode of delivery, and maternal complications of interest are presented in Table 2. There were no significant differences between the 2 study groups. Neonatal assessments immediately after delivery, including Apgar scores and body measurements, were comparable in the rhAT and placebo groups. The mean birthweight was 1056.9 g (standard deviation [SD], 508.16) in the rhAT group and 1177.4 g (SD, 572.93) in the placebo group.

Primary and secondary outcomes

For the primary outcome, there was no significant difference in the median increase in GA between treatment groups (5.0 days [range, 0–75] in the rhAT group and 6.0 days [range, 0–85] in the placebo group; P=.95). For the secondary outcome, there was no significant difference between treatment groups in the mean composite fetal or neonatal outcome score. The mean composite fetal or neonatal outcome score was 0.7 (SD, 1.0) in the rhAT group and 0.6 (SD, 0.9) in the placebo group (Tables 3 and 4). There was no difference in the median increase in gestational days gained between the rhAT and placebo groups when the

TABLE 1
Maternal demographics and baseline clinical characteristics

Parameter	rhAT (n=61)	Placebo (n=58)
Age at screening (y)		
Mean (SD)	29.0 (6.1)	29.3 (6.7)
Median	29.0	30.0
Minimum to maximum	18–50	18–44
Mean (SD)	27.18 (1.96)	27.34 (2.06)
Median	27.29	27.57
Minimum to maximum	23.1–30.0	23.0–30.0
GA at randomization, n (%)		
23 wk (23 0/7–23 6/7)	4 (6.5)	3 (5.2)
24 wk (24 0/7–24 6/7)	5 (8.1)	6 (10.3)
25 wk (25 0/7–25 6/7)	9 (14.5)	6 (10.3)
26 wk (26 0/7–26 6/7)	8 (12.9)	7 (12.1)
27 wk (27 0/7–27 6/7)	11 (11.7)	12 (20.7)
28 wk (28 0/7–28 6/7)	11 (11.7)	5 (8.6)
29 wk (29 0/7–29 6/7)	13 (21.0)	16 (27.6)
30 wk (30 0/7–30 6/7)	1 (1.6)	3 (5.2)
Race, n (%)		
Asian	2 (3.2)	1 (1.7)
African American	27 (43.5)	27 (46.6)
Native American	1 (1.6)	0 (0.0)
White	29 (46.8)	30 (51.7)
Other	3 (4.8)	0 (0.0)
Ethnicity, n (%)		
Hispanic	6 (9.7)	10 (17.2)
Not Hispanic	56 (90.30)	48 (82.8)
Type of preeclampsia, n (%)		
Preeclampsia	39 (62.9)	32 (55.2)
Superimposed preeclampsia	23 (37.1)	26 (44.8)
BMI (kg/m^2)		
Mean	36.92 (10.20)	35.86 (7.84)
Median	34.87	35.61
Minimum to maximum	21.3–67.8	19.7–58.3

BMI, body mass index; *GA*, gestational age; *rhAT*, recombinant human antithrombin; *SD*, standard deviation.
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groups were stratified at randomization based on the diagnosis of PE vs superimposed PE; presence or absence of proteinuria; or presence or absence of severe-range blood pressures (BPs). Subgroup analyses of modified intent-to-treat population (ITT), defined as all women in the ITT population who received any study treatment, or per-protocol population, defined as patients who completed the study without any major protocol deviations, did not indicate significant differences between treatment groups.

Compliance and adverse events

Most women completed the study drug treatment (82% overall), with a slightly higher proportion of study drug completion in the rhAT group (90%) than the placebo group (72%). Similar proportions of neonate subjects in each study group completed the study (93% overall). There were no differences in maternal adverse events between treatment groups. The most frequently observed maternal treatment-emergent adverse events (TEAEs) in both treatment groups were worsened hypertension (rhAT, 53.3%; placebo, 46.3%) and headache (rhAT, 40.0%; placebo, 35.2%). No fetus experienced a TEAE that the investigator considered to be related to the study drug. There were no fetal deaths. Among neonates, at least 1 serious adverse event was experienced by 53.3% of neonates in the rhAT group and 44.4% of neonates in the placebo group. A total of 5 neonates died, of whom 3 were in the rhAT group and 2 were in the placebo group. No neonate experienced a serious adverse event or death that the investigator considered to be related to the study drug.

RhAT administration was not associated with an increased risk of bleeding. The estimated blood loss after delivery was 500 to <1000 cc for most subjects in each group (rhAT, 43 subjects [69.4%]; placebo, 34 subjects [59.6%]), and only 2 subjects (3.2%) (both in the rhAT group) had an estimated blood loss of ≥1500 cc. Mean changes from the baseline for prothrombin time and activated partial thromboplastin time were comparable between the rhAT and placebo groups. No statistically significant differences between the treatment groups in mean changes from the baseline in coagulation parameters were observed. Overall, there was a low rate of transfusion (3 [4.8%] and 0 [0%]) in the rhAT and placebo groups, respectively, which was well within the accepted previous published experience.

Antithrombin activity

At baseline, the 2 treatment groups had a similar mean AT activity (%) (rhAT,

TABLE 2
Delivery information (ITT population)

Parameter	rhAT (n=62)	Placebo (n=58)
GA at time of delivery (wk)		
Mean (SD)	28.77 (2.66)	29.64 (3.24)
Median	28.79	29.64
Minimum to maximum	24.0–34.9	23.1–40.0
Indications for delivery (maternal, fetal, or both), n (%)		
Maternal	43 (69.4)	40 (69.0)
Fetal	5 (8.1)	9 (15.5)
Both	14 (22.6)	9 (15.5)
Indications for delivery, n (%)		
>34 wk gestation	3 (4.8)	6 (10.3)
Refractory hypertension despite maximal medical intervention	36 (58.1)	28 (48.3)
HELLP	1 (1.6)	0 (0.0)
Thrombocytopenia	5 (8.1)	1 (1.7)
Elevated liver enzymes	10 (16.7)	4 (7.1)
Elevated LDH	5 (8.3)	1 (1.8)
Elevated total bilirubin	0 (0.0)	0 (0.0)
Oliguria with evidence of acute renal failure	0 (0.0)	0 (0.0)
Persistent visual symptoms	0 (0.0)	2 (3.4)
Placental abruption	0 (0.0)	0 (0.0)
Oligohydramnios	2 (3.2)	2 (3.4)
IUGR below fifth percentile	1 (1.6)	0 (0.0)
Pulmonary edema	2 (3.2)	3 (5.2)
Reverse end-diastolic flow on umbilical Doppler ultrasound	2 (3.2)	1 (1.7)
Biophysical score of ≤4/10 on 2 occasions	0 (0.0)	1 (1.7)
Nonreassuring fetal heart rate tracing	15 (24.2)	12 (20.7)
Intractable headache unrelieved with analgesia	8 (12.9)	10 (17.2)
Intractable right upper quadrant abdominal pain or vomiting	5 (8.1)	1 (1.7)
Other	17 (27.4)	14 (24.1)
Maternal complications of interest		
Eclamptic seizure	0 (0.0)	1 (1.7)
HELLP	1 (1.6)	0 (0.0)
Oliguria with evidence of acute renal failure	0 (0.0)	0 (0.0)
Pulmonary edema	2 (3.2)	3 (5.2)
Stroke	0 (0.0)	0 (0.0)
Mode of delivery, n (%)		
Vaginal delivery	5 (8.1)	11 (19.0)
Cesarean delivery	57 (91.9)	47 (81.0)
Blood transfusion required within 24 h after delivery, n (%)	3 (4.8)	0 (0.0)

GA, gestational age; *HELLP*, hemolysis, elevated liver enzymes, and low platelet; *ITT*, intent to treat; *IUGR*, intrauterine growth restriction; *LDH*, lactate dehydrogenase; *rhAT*, recombinant human antithrombin; *SD*, standard deviation.

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TABLE 3
Secondary outcome: composite endpoint of fetal and neonatal outcomes (ITT)

Parameter population statistic	rhAT (n=60)	Placebo (n=56)	Difference (rhAT−placebo)	Adjusted difference, 95% CI (rhAT−placebo)	*P* value
Composite endpoint of fetal and neonatal outcomes					
Mean (SD)	0.7 (1.0)	0.6 (0.9)	0.1	0.0 (−0.3 to 0.4)	.7824
Median	0.0	0.0	—	—	—
Minimum to maximum	0−4	0−4	—	—	—

Fetal and neonatal events include BPD, IVH (grade ≥3), cystic PVL, ROP (stage ≥3), late sepsis, and NEC (Bell's stage ≥2). Scores: 0, no events, no mortality; 1, 1 event, no mortality; 2, 2 events, no mortality; 3, 3 or more events, no mortality; 4, death. The secondary efficacy endpoint is a composite endpoint of specific fetal and neonatal outcomes consisting of BPD, IVH, PVL, ROP, late sepsis, NEC, and mortality (fetal and neonatal). Multiple imputation methods were used for the imputation of any missing data for the secondary efficacy endpoint. The regression model included treatment, type of PE (PE vs superimposed PE), and GA at randomization (measured in days as a continuous variable). For subjects for whom both 36-week PMA and the 36-week PMA visit occurred in <28 days after delivery, the secondary outcome endpoint includes events occurring during the 4−6 week postdelivery visit.

BPD, bronchopulmonary dysplasia; *CI*, confidence interval; *GA*, gestational age; *ITT*, intent to treat; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PE*, preeclampsia; *PMA*, postmenstrual age; *PVL*, periventricular leukomalacia; *rhAT*, recombinant human antithrombin; *ROP*, retinopathy of prematurity; *SD*, standard deviation.

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94.70 [SD, 14.60]; placebo, 93.05 [SD, 14.29]). Maximum AT activity (%) in the rhAT group was 291.7 (observed at day 8). A total of 15 patients had baseline AT levels below 80% (8 in the rhAT group and 7 in the placebo group), and their results were consistent with the overall results of the study. The mean AT activity in umbilical cord blood was 28.25 (SD, 8.63) in the rhAT group and 31.44 (SD, 14.46) in placebo group subjects, indicating that rhAT did not cross the placenta.

Comment

The key findings of our study are as follows: (1) rhAT administration to women with singleton gestation diagnosed as having PPE between 23 and 30 weeks' gestation did not extend their pregnancy more than the expectant management alone; (2) the median increase in GA was 5.0 days in the rhAT group and 6.0 days in the placebo group; (3) rhAT administration did not improve individual or composite fetal or neonatal outcomes; and (4) there were no safety issues related to rhAT administration in the setting of PPE, despite supraphysiological AT levels and prolonged administration.

In our study, the rhAT and placebo groups were generally well balanced at baseline. The treatment groups had a similarly high mean body mass index (BMI) at screening (36−37 kg/m^2). We do acknowledge that there were some potentially important differences in the respective treatment group profiles at baseline. For example, there were differences between the groups in obstetrical history. The percentage of first-time pregnancies was higher in the rhAT group (37%) than the placebo group (22%), with an even greater difference in the number of subjects who had no previous live births (rhAT, 60%; placebo, 28%), corresponding with higher rates of previous neonatal morbidity, miscarriage, and abortion in the rhAT group. The mean number of previous live births in the placebo group was double than that of the rhAT group (rhAT, 0.7; placebo, 1.4). Of the subjects who did have previous deliveries, the mean minimum GA for previous deliveries was 4 weeks less in the rhAT group in comparison with the placebo group (31 weeks vs 35 weeks). The intrauterine growth restriction at baseline was more frequent in the rhAT group than the placebo group (27% vs 19%, respectively). These data suggest a more severe obstetrical history among subjects from the rhAT group. In contrast, the percentage of subjects who had previously experienced PE was lower in the rhAT group than the placebo group (28% and 40%, respectively). Although the diagnostic criteria used for subjects with superimposed PE were comparable between groups, women in the rhAT group who were diagnosed as having PE may have been in a more severe condition at the time of diagnosis than subjects in the placebo group. In the superimposed PE subgroup, nearly twice as many patients in the rhAT group were diagnosed as having the criteria of severe gestational hypertension than the placebo group (17 vs 9, respectively). In addition, the mean systolic and diastolic BP used for diagnosis was higher in the rhAT group (rhAT, 165.2/97.5 mm Hg; placebo, 159.1/95.7 mm Hg). Ten patients in the rhAT group developed thrombocytopenia or hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome compared with 2 patients in the placebo group. Overall, these few differences between the rhAT and placebo are unlikely to account for the lack of efficacy of rhAT in prolonging gestation in this trial. We were unable to detect any benefit of rhAT administration in any PE subgroup.

The efficacy results in our trial are not consistent with earlier results from the Maki study in Japan[18] that showed a significant and clinically relevant prolongation of pregnancy of approximately 1 week with AT replacement (16.8 days vs 10.2 days for the placebo group). The Maki study and the current study population differed in background characteristics, most notably in GA difference, racial composition, and BMI, which were substantially higher in our study. In the Maki study, the mean GA in the AT-treated and placebo groups at randomization was 31.8 (SD, 3.2) and 31.7 (SD, 2.7) weeks, respectively, which was nearly 1 month later than that in our study population. In the Maki study,[18] patients diagnosed as having PE between 24 to 35 weeks' gestation were included if the patients experienced a systolic BP of ≥160 mm Hg and/or

diastolic BP of ≥110 mm Hg and/or proteinuria of ≥2 g/L of protein in a 24-hour urine collection and a Gestosis Index of ≥ 6 on 2 occasions at least 6 hours apart despite bed rest. Patients with chronic hypertension, renal disease, diabetes mellitus, systemic lupus erythematosus, multiple pregnancy, and other severe medical conditions were excluded. Patients with AT deficiency were also excluded. Compared with our study, Maki et al[18] included patients at a later GA and required higher BPs.

Other supportive evidence for the use of AT replacement in PPE came from the study of Paternoster et al[21] who found that higher doses of AT replacement in patients with severe PE between 24 and 33 weeks' gestation were associated with greater prolongation of pregnancy. In the Paternoster study,[21] subjects diagnosed as having PE between 24 to 33 weeks were included in the study on the basis of the following criteria: diastolic arterial pressure of >90 mm Hg and systolic arterial pressure of >140 mm Hg on more than 3 occasions, proteinuria (in a 24-hour urine sample) of >0.3 g/L, and AT of ≤75%. Patients with chronic hypertension, renal disease, diabetes mellitus, systemic lupus erythematosus, multiple pregnancies, and other severe medical conditions were excluded. Compared with our study, Paternoster et al[21] included patients at a later GA and required decreased AT activity for enrollment.

Toward the end of our study, D'Angelo et al[24] reported on a multicenter randomized trial with negative results, using high-dose AT replacement in PPE. These investigators had planned to enroll 240 patients from 13 centers but only enrolled 38 patients; the sponsor terminated the trial because of poor enrollment. In the D'Angelo study,[24] patients diagnosed as having PE at <30 weeks' gestation were included. The criteria for the diagnosis of PE were diastolic BP repeatedly at >90 mm Hg plus a daily proteinuria of ≥0.3 g. The exclusion criteria were conditions requiring immediate delivery. Compared with our study, D'Angelo et al[24] included patients at a similar GA and did not require decreased AT activity for enrollment, which was similar to our study. In our study, we enrolled singleton patients with PE diagnosed between 23 to 30 weeks' gestation who were being expectantly managed. We included patients with chronic hypertension, and AT levels were not a criterion for entry into the study. We excluded patients with multiple gestation.

We found that baseline AT activity levels were higher than expected, consistent with the findings of the D'Angelo study and at odds with the Maki study and the initial study describing AT activity in PE.[25] D'Angelo et al[24] found normal mean (SD) AT activity levels at baseline in most randomized patients with PE (88%±16% and 85%±85% for the patients receiving AT and placebo, respectively). Peak AT activity levels in our study were consistent with the Maki study, which found a peak plasma AT activity of 200% immediately after the AT infusion, and the D'Angelo study (244%). Hence, insufficient dosing is unlikely to account for our negative efficacy results and the study by D'Angelo. Moreover, our continuous daily infusion of rhAT would also have mitigated against AT elimination losses previously reported in patients with PE.[19]

Another consideration that might explain our negative findings is the lack of homogeneity of our patient population. Just before the study started, the ACOG released new diagnostic criteria for PE.[6] We incorporated the new criteria into our current protocol. Proteinuria was no longer required for the diagnosis of PE. The median prolongation of pregnancy in the subgroup of patients without proteinuria at baseline was 24 days in contrast to 5 days in the group that had proteinuria.

Another possibility for the lack of effect in our study may be related to the timing of study drug administration in relation to the clinical status of the patient and when the patient was admitted to the hospital. It is possible that the delay in the timing of study drug administration affected the ability to detect a treatment difference. Owing to enrollment challenges, the GA was extended to ≤30 weeks. Consequently, the overall rate of neonatal morbidity was quite low, and the mean composite score was <1.

Limitations

Although 23 sites participated in the trial, only 7 (30%) enrolled more than 5 patients, which attests to the challenge of an interventional trial in a pregnant population with a relatively rare disease. Initial enrollment into the trial was slow, so the upper limit of GA inclusion criteria was extended from 28 to 30 weeks in an effort to accelerate study enrollment. However, this change contributed to a very low neonatal composite score. It would have been difficult to show a neonatal benefit even if rhAT extended pregnancy significantly. The diagnosis of PE was based on the definition of PE in place at the time, which allows for some patients to be diagnosed as having PE based on subjective criteria (eg, severe headache) along with BP criteria. Another potentially challenging diagnostic criterion relates to the BP criteria for superimposed PE. The guidelines suggested that "a sudden increase in blood pressure that was previously well controlled" satisfies the PE criteria,[6] which is imprecise. We insisted on an increase in BP requiring either a start of an antihypertensive agent, increasing the dose of a current agent, or adding a second agent, which increased the likelihood of correctly identifying patients with superimposed PE.

Strengths

The PRESERVE-1 trial represents the largest, most comprehensive study of PPE ever completed in the United States. The trial was completed in <2 years, which is remarkable considering the rarity of the patient population and the operational complexity of the trial design. The study was adequately powered to address the primary outcome. An adaptive study design enabled a sample size reestimation. Only principal investigators and centers comfortable with expectant management participated in the trial. The study inclusion and exclusion criteria were based on the current guidelines at the time.[5,6] The

TABLE 4
Fetal or neonatal outcomes of specific interest

Parameter	rhAT (n=62), n (%)	Placebo (n=58), n (%)	Difference (%) (rhAT−placebo)	Odds ratio (95% CI) (rhAT−placebo)	*P* value
Fetal death (including stillbirth)	0 (0.0)	0 (0.0)	0.0	N/A	—
Neonatal death	3 (4.8)	2 (3.4)	1.4	1.541 (0.197−12.033)	.6799
SGA of <10%	12 (19.4)	9 (15.5)	3.9	1.384 (0.514−3.726)	.5201
RDS	59 (95.2)	51 (87.9)	7.3	2.724 (0.665−11.154)	.1635
BPD	22 (35.5)	20 (34.5)	1.0	0.989 (0.456−2.142)	.9774
ROP stage ≥3	0 (0.0)	0 (0.0)	0.0	N/A	—
NEC (Bell's grade ≥2)	1 (1.6)	2 (3.4)	−1.8	0.493 (0.043−5.642)	.5692
IVH ≥3	3 (4.8)	1 (1.7)	3.1	2.606 (0.257−26.460)	.4179
Cystic PVL	2 (3.2)	1 (1.7)	1.5	1.250 (0.101−15.475)	.8618
Early sepsis (positive blood culture not regarded as contaminant within 72 h of delivery)	0 (0.0)	0 (0.0)	0.0	N/A	—
Late sepsis (positive blood culture not regarded as contaminant >72 h of delivery)	2 (3.2)	4 (6.9)	−3.7	0.540 (0.060−3.232)	.5001
Meningitis	0 (0.0)	1 (1.7)	−1.7	N/A	.9441
Avoidance of neonatal morbidity (BPD, IVH grade ≥3, cystic PVL, ROP stage ≥3, late sepsis, and NEC Bell's grade ≥2) and of fetal or neonatal mortality	6 (58.1)	33 (56.9)	1.2	1.114 (0.521−2.382)	.7813

For subjects who did not complete the study, data up to their discontinuation were used. The odds ratio and 95% CI and the *P* value are for the treatment effect from a logistic regression model in terms of treatment, type of preeclampsia (preeclampsia vs superimposed preeclampsia), and GA at randomization.

BPD, bronchopulmonary dysplasia; *CI*, confidence interval; *IVH*, intraventricular hemorrhage; *N/A*, not available; *NEC*, necrotizing enterocolitis; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome; *rhAT*, recombinant human antithrombin; *ROP*, retinopathy of prematurity; *SGA*, small for gestational age.

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decision to deliver was made uniquely by a maternal-fetal medicine specialist. The assumptions underlying the pharmacokinetic modeling were proven to be accurate. This trial establishes the safety of rhAT in PPE even with supraphysiological levels of rhAT.

Conclusion

The administration of rhAT to women with singleton pregnancy diagnosed as having early-onset PE between 23 and 30 weeks' gestation was not associated with pregnancy prolongation and improvement in maternal or neonatal outcomes. rhAT is safe for pregnant women with PPE and their fetus or neonates.

Given the conflicting results regarding AT supplementation in PPE, additional studies are indicated to determine its potential benefit in this vulnerable patient population. Nulliparous women with singleton gestation, without preexisting chronic hypertension or other medical conditions, diagnosed as having PE between 23 and 28 weeks with AT activity levels of <80% would constitute the ideal patient population in a randomized clinical trial to determine whether rhAT antenatal administration will prolong gestation. ■

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SUPPLEMENTAL TABLE 1
A priori fetal or neonatal outcomes of specific interest

Perinatal complication	Definition
Fetal death	Includes stillbirth
Neonatal death	Death from day 0 (not stillbirth) to the last study assessment
All death	Fetal and neonatal death
SGA	Below the tenth percentile weight by gender from Fenton et al[26]
RDS	Clinical features of RDS and oxygen or respiratory support for ≥6 h of the first 24 h of life
BPD	Oxygen requirement at 36 wk postmenstrual age
ROP	Severe (≥stage 3) retinopathy of prematurity
NEC	Bell's stage ≥2
IVH	Cranial ultrasound, CT, or MRI evidence for IVH grade ≥3
Cystic PVL	Cranial ultrasound, CT, or MRI evidence for cystic PVL
Early sepsis	Early sepsis (positive blood culture not regarded as contaminant), within 72 h of delivery
Late sepsis	Late sepsis (positive blood culture not regarded as contaminant) more than 72 h after delivery
Meningitis	Positive culture of cerebrospinal fluid

BPD, bronchopulmonary dysplasia; *CT*, computed tomography; *IVH*, intraventricular hemorrhage; *MRI*, magnetic resonance imaging; *NEC*, necrotizing enterocolitis; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome; *ROP*, retinopathy of prematurity; *SGA*, small for gestational age.

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SUPPLEMENTAL TABLE 2
A priori maternal outcomes of specific interest

Maternal complication	Definition
Maternal death	Documented death of any cause during the trial up to 28 d after delivery
Eclamptic seizure	Presence of new-onset grand mal seizures in a woman with preeclampsia, without evidence for other etiology (eg, bradycardia, tachycardia, hypotension, expected or unexpected drug effect)
Myocardial infarction	Detection of a rise and/or fall of cardiac biomarker values (cardiac troponin) with at least 1 value above the 99th percentile upper reference limit and with at least one of the following: • Symptoms of ischemia • New or presumed new significant ST-segment T-wave (ST-T) changes or new left bundle branch block • Development of pathologic Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy
CVA	Acute onset of a focal neurologic deficit, with CT or MRI evidence for hemorrhagic CVA or cerebral infarction (brain or retinal cell death caused by prolonged ischemia)
Transient ischemic attack	A brief episode (usually less than 1 or 2 h) of neurologic dysfunction caused by focal brain or retinal ischemia without evidence of acute infarction (as determined by CT or MRI)
Progressive renal insufficiency	• Serum creatinine of >1.1 mg/dL
Thrombocytopenia (without HELLP)	• Platelet count of $<100{,}000/\mu$L
HELLP	A combination of: • AST of ≥ 70 IU/L • Platelet count of $<100{,}000/\mu$L • Evidence of hemolysis on blood film plus either LDH of ≥ 600 IU/mL or total bilirubin of ≥ 1.2 mg/dL
DIC	Overt DIC is defined as a score of ≥ 5 derived from scoring the following parameters: • Platelet count of $\geq 100/mm^3$ (0), $\geq 50/mm^3$ but $<100/mm^3$ (1), $<50/mm^3$ (2) • Elevated fibrin-related marker such as soluble fibrin monomer or fibrin degradation products with no increase (0), moderate increase (2), strong increase (3) • Prolonged PT of ≤ 3 s (0), >3 but <6 s (1), and ≥ 6 s (2) • Fibrinogen level of ≥ 1.0 g/L (0) and <1.0 g/L (3)
Pulmonary edema	Clinical symptoms of pulmonary edema, confirmed by chest x-ray examination
Placental abruption	Vaginal bleeding and uterine pain or tenderness accompanied by documented fetal distress or uterine hypertonicity
Severe intra- and postpartum hemorrhage	Estimated blood loss of ≥ 1500 mL within 24 h after delivery
VTE including DVT and pulmonary embolism	Clinically symptomatic VTE (eg, breathlessness, hemoptysis, leg pain, and swelling) with confirmation by appropriate diagnostic tools (eg, venography, Doppler ultrasound, ventilation or perfusion scan, MRI)

AST, aspartate aminotransferase; *CT*, computed tomography; *CVA*, cerebrovascular accident; *DIC*, disseminated intravascular coagulation; *DVT*, deep vein thrombosis; *ECG*, electrocardiogram; *HELLP*, hemolysis, elevated liver enzymes, and low platelet; *LDH*, lactate dehydrogenase; *MRI*, magnetic resonance imaging; *PT*, prothrombin time; *VTE*, venous thromboembolism.

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SUPPLEMENTAL BOX
Exclusion criteria

Criteria requiring immediate delivery of the fetus before randomization:

- Refractory hypertension despite maximal medical intervention of systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥110 mm Hg
- Thrombocytopenia (platelets <100,000/μL) with or without HELLP syndrome, defined as:
  - AST of ≥70 units/L
  - Platelet count of <100,000/μL
  - Evidence of hemolysis on blood film plus either LDH of ≥600 IU/mL or total bilirubin of ≥1.2 mg/dL; oliguria (≤500 mL/24 h)
  - Evidence of progressive renal insufficiency
- Serum creatinine concentration of >1.1 mg/dL
- Persistent visual disturbances
- Placental abruption
- Pulmonary edema
- Nonreassuring fetal heart rate tracing
- Intractable headache unrelieved with analgesia
- Intractable right upper quadrant abdominal pain or vomiting
- If umbilical Doppler ultrasound had been performed, the presence of an abnormal umbilical artery Doppler as defined by persistent, absent, or reverse end-diastolic flow
- Biophysical score of ≤4/10 on 2 occasions
- Oligohydramnios (deepest vertical pocket of <2×2 cm on ultrasound)
- Other maternal or fetal conditions that would preclude expectant management

Other exclusion criteria:

- Known lethal or major fetal anomaly
- Recent (within 12 mo) history of maternal alcoholism or drug dependence
- Diagnosis of epilepsy
- Need for chronic therapy with NSAIDs including selective Cox-2 inhibitors, or unwilling to abstain from the use of NSAIDs during the study treatment period (low-dose aspirin of 81 mg/d or less was allowed)
- Received within 72 h or had requirement for heparin
- Low-molecular-weight heparin such as enoxaparin or dalteparin
- Fondaparinux
- Antiplatelet agents such as clopidogrel, prasugrel, or high-dose aspirin (>81 mg/d)
- DTIs such as dabigatran
- Preexisting renal disease, documented prepregnancy or in pregnancy before 20 wk gestation (before the diagnosis of preeclampsia), or 24 h urine of ≥0.3 g/24 h, documented in pregnancy, before 20 wk gestation, or ≥2+ dipstick or ≥0.3 PCR, documented in pregnancy at the last available test before 20 wk gestation
  - In the case of conflicting results between dipstick, PCR, and timed urine collection to work up an episode of proteinuria, the timed urine collection result would supersede other results.
- Multifetal pregnancy
- History of antiphospholipid antibody syndrome
- Known hypersensitivity to goat and goat milk proteins
- Participation in another interventional clinical trial of an investigational, unapproved therapy (drug, biologic, device) within 30 d of consent

AST, aspartate aminotransferase; *Cox*, cyclooxygenase; *DTI*, direct thrombin inhibitor; *HELLP*, hemolysis, elevated liver enzymes, and low platelet; *LDH*, lactate dehydrogenase; *NSAID*, nonsteroidal antiinflammatory drug; *PCR*, polymerase chain reaction. *Paidas et al. Recombinant AT vs placebo in preterm preeclampsia. Am J Obstet Gynecol 2020.*