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High dose antithrombin supplementation in early preeclampsia: A randomized, double blind, placebo-controlled study☆

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ABSTRACT

Introduction: Antithrombin levels are often reduced in preeclampsia and infusion of antithrombin concentrates has been reported to prolong gestation in severe preeclampsia. We aimed to evaluate efficacy and safety of high-dose antithrombin (ATIII) supplementation in patients with single pregnancies and preeclampsia occurring before 30 weeks of gestation.
Materials and methods: In November 2004 a double-blind, placebo-controlled trial (code KB033) was started in 13 Italian centers. The planned sample size was of 240 patients (intention-to-treat, ITT population) to detect a 30% relative risk reduction of the primary endpoint, composite perinatal morbidity. Eligible patients were randomized to high dose AT (3000 IU/daily, ATIII Kedrion S.p.A., Italy), or placebo (1% glycine) for 7 days or less until delivery, whichever came first. The per-protocol (PP) population was restricted to patients receiving at least two days of treatment.
Results: The study was terminated by the sponsor in October 2007 after the enrolment of 38 evaluable patients – 20 randomized to high dose AT and 18 to placebo, 27 treated for 2 days or more – out of 164 screened patients. Enrolment failures were mainly represented by requirement for immediate delivery and consent refusal (91 patients). The primary endpoint occurred in 15 of 38 patients (39.5%), with a relative risk in the AT arm of 0.85 (95% CI 0.42–1.75) and 0.79 (95% CI 0.30-2.11) in the ITT and PP populations, respectively. Living neonates in the two arms had similar weight at birth, Apgar scores, and duration of hospitalization in neonatal ICU. In mothers, AT supplementation was associated with reduced blood loss at delivery and with surrogate laboratory markers (LDH, *d*-dimer).
Conclusions: The results of this markedly underpowered trial, albeit suggestive of a potential maternal benefit, cannot support high-dose AT supplementation to improve fetal/neonatal outcomes in early preeclampsia.
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1. Introduction

A significant reduction in levels of antithrombin (AT) is frequently found in pre-eclampsia, with antithrombin levels possibly correlated with maternal and fetal morbidity [1]. The elimination half-life of transfused AT concentrate is reduced to 8.5 h in preeclamptic women who have mean baseline AT activity of 71% [2]. Low AT activity in preeclampsia appears mainly due to increased consumption [1, 3–5], but impaired liver function [5] and urinary loss [6] have also been shown to play a role. After the successful treatment with AT concentrate of a preeclamptic patient with severe AT deficiency [7], a series of pilot studies, also supported by animal studies [8, 9], suggested that administration of AT may have a clinical benefit in patients with preeclampsia [10–13]. A double-blind, randomized, placebo-controlled trial evaluated whether treatment with high-dose AT concentrate (Kybernin® HS, 3000 IU for 7 days) could improve the clinical and perinatal outcome in patients with severe preeclampsia [14]. In this study, gestation was significantly prolonged by about 7 days ($p = 0.007$) and the number of low-birth weight infants significantly reduced ($p = 0.011$) in the AT group; however no effect on fetal/neonatal mortality was observed [14]. A feasibility study published three years later by the same study group randomized patients with severe preeclampsia, all treated with i.v. prophylactic UFH, to receive AT concentrate (1500 U daily for 7 consecutive days) or not [15]. The AT plus heparin group fared significantly better than the heparin alone group, and the authors concluded that AT alone might be effective enough for severe preeclampsia [15].

Fetal/neonatal mortality is about 10% in late preeclampsia, but is on average 30% in preeclampsia occurring before the 30th week of gestation [16], given the clear relationship between gestational age, birth weight and perinatal outcome [17]. Knowledge that fetal outcomes are poor in early preeclampsia together with evidence that AT

☆ The study protocol KB033 (ATIII-EPAS) received final approval from the Ethical Committee of the Scientific Institute San Raffaele on December 4th, 2003.

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concentrate supplementation may prolong pregnancy in this setting led us to promote a multicenter double blind study to evaluate the efficacy on fetal and neonatal outcome of high-dose AT concentrate supplementation in early preeclampsia (<30th week of gestation).

2. Patients and methods

2.1. Study design

In November 2004 a randomized, double-blind, placebo-controlled trial (EPAS-ATIII, Early Pre-eclampsia Antithrombin Study, code KB033, sponsored by Kedrion Biopharmaceuticals, Castelvecchio Pascoli, Italy), was started after obtaining approval by the Ethics Committees of the 13 Italian Centers involved in the study. Inclusion criteria were age ≥ 18 years, signed informed consent, and single pregnancy complicated by preeclampsia occurring before the 30th week of gestation and not requiring urgent delivery. Criteria for diagnosis of pre-eclampsia were diastolic blood pressure repeatedly >90 mm Hg at 2 measurements 6 h apart plus a daily proteinuria ≥0.3 g – replaced by dipstick ++ or protein content >0.1 g/dL in a urine sample [18]. Exclusion criteria were age < 18 years, conditions requiring immediate delivery (severe hypertension resistant to treatment, eclampsia, pulmonary edema, deterioration of renal function with creatinine >1.2 mg/dL associated with treatment-resistant oliguria [19]), pre-existing diabetes, known thrombophilia or connective tissue disorder requiring prophylactic treatment with unfractionated heparin, low molecular weight heparin (LMWH) or fondaparinux, known kidney disease, ongoing anticoagulant treatment, participation in other interventional study during the same pregnancy. Patients with history of preeclampsia on prophylactic LMWH could be enrolled 12 h after the last administration; the use of antiplatelet drugs of any kind was allowed.

Eight centers recruited eligible patients in the study (Appendix A); within 12 h from diagnosis patients were randomized to receive either ATIII Kedrion (daily boluses of 3000 IU, dissolved in injectable water, 60 mL) or undistinguishable placebo (injectable water containing 1% glycine, 60 mL) for 7 days or until delivery, whichever came first. Choice of glycine as placebo was because it is also contained within the AT preparation at a concentration of 0.75% and transfers to the fetus significantly less than other amino acids.

The primary efficacy outcome was the composite perinatal morbidity (perinatal mortality plus neonatal severe morbidity), inclusive of proliferative obliterans retinopathy (ROP) grade III—IV, intraventricular hemorrhage (ICH) grade III—IV, necrotizing enterocolitis (NEC) requiring surgery, peri-ventricular leukomalacia, severe respiratory distress syndrome (RDS), bronchodysplasia, and neonatal severe sepsis [20]. Secondary efficacy outcome were: a) the occurrence of pre- and post-partum maternal complications, defined as death, need for Intensive Care Unit admission, placental detachment, eclampsia, cerebrovascular complications, pulmonary edema/acute RDS, renal or hepatic complications, venous thromboembolism, disseminated intravascular coagulation; b) type of delivery, placental weight, weight at birth, Apgar score, pH of umbilical arterial blood; c) time spent in the Neonatal Intensive Care Unit; d) serial maternal (blood pressure, 24-h urinary output, and local laboratory parameters, see below) and fetal-neonatal parameters (estimated weight by ultrasound, presence of intrauterine growth retardation, biophysical profile [20], venous base deficit, umbilical and uterine Doppler examination). Safety outcomes were blood loss at delivery, allergic reactions caused by the IMP, and other adverse events, inclusive of death.

2.2. Sample size calculation

Frequency of pre-eclampsia ranges between 2% and 7% in healthy nulliparous women [22], with a 0.38% rate of preeclampsia occurring before or at 33 weeks of gestation [23]. In the preeclamptic population of the Scientific Institute San Raffaele from 1990 to 1997, the combination of mortality and severe fetal/neonatal morbidity had an incidence of 61.3% for pre-eclampsia occurring before the 30th gestational week, with a clear trend for a higher incidence of serious maternal complications before 28 weeks of gestation. The planned sample size was set to 120 patients per arm. This would have allowed, with the active treatment, detection of a 30% relative risk reduction in the primary efficacy endpoint with power (β error) of 0.8 and α error of 0.05 assuming a 60% incidence of the primary outcome in the placebo arm, and a 50% or greater relative risk reduction with an incidence as low as 30% of the primary outcome in the placebo arm.

2.3. Randomization and blinding

Randomization and data collection was through a website managed by GB Pharma Consulting Service, Pavia, Italy. Randomization was in blocks of 5 stratified for gestational age below or above the 28th week. To ensure blinding, packaging of products was to prevent their identification by the investigator. AT and placebo were supplied in identical brown bottles and were administered after reconstitution with a dedicated infusion set. Local AT measurements were not permitted except for emergency situations. Patients, local investigators and monitors were not aware of the allocation to treatment until completion of the study and until complete entry of data into the database.

2.4. Laboratory tests

Local examination of the maternal hematological and blood chemistry profile (hemoglobin, hematocrit, red blood cell (RBC), white blood cell (WBC) and platelet count, s-aspartate aminotransferase (s-AST), s-alanine aminotransferase (s-ALT), total and conjugated s-bilirubin, s-uric acid, s-lactate dehydrogenase (s-LDH), prothrombin time (PT) and activated partial thromboplastin time (aPTT) ratios, p-fibrinogen, s-creatinine and daily proteinuria) was performed before randomization, on day 1, 4 and 7 of treatment, before delivery and 48 h after delivery.

As an ancillary study, centralized laboratory tests on maternal citrated blood samples serially collected as above from day 1 of treatment until 48 h after delivery, centrifuged, aliquoted and stored locally at −30 °C, were performed at Laboraf S.p.A (Milano, Italy), inclusive of AT, *d*-dimer (DD), protein C (PC) and protein S (PS) anticoagulant activity, soluble thrombomodulin (sTM) (Stago, Asniere sur Seine, France), thrombin–antithrombin complex (TAT), tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6, Bender MedSystems, Vienna, Austria), plasminogen activator inhibitor-2 (PAI-2, Imubind, American Diagnostica, Stamford, CT, US), and activated protein C (aPC). The latter was measured as described by Liaw et al. [21] on plasma samples from blood collected in tubes containing sodium citrate (3.2%) and benzamidine-HCl (200 mM). Antithrombin determinations were also performed on plasma samples obtained 60 min after the bolus administration of AT concentrate or placebo on days 1, 4, and 7.

2.5. Statistical analysis

The statistical plan included descriptive statistic, and evaluation of the treatment effects for both intention-to-treat (efficacy and safety outcomes) and per-protocol (efficacy outcomes) populations, the latter restricted to patients who had received AT or placebo for at least 2 days prior to delivery. An interim analysis was planned after the enrolment of 120 patients. The Cochran–Mantel–Haenszel test was used to compare the absolute frequencies of the primary endpoint in the two treatment groups adjusted for gestational age and any concomitant medication. The relative risk (RR) and the corresponding joint 95% confidence interval (CI) were estimated, along with the relative risks within the arm and their homogeneity, using the Breslow–Day test. A similar analysis was carried out on the RR of the secondary endpoints. The prolongation of pregnancy was analyzed with the Cox model entering the gestational

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