INVESTIGATIONAL RNAI THERAPEUTIC TARGETING ANGIOTENSINOGEN (AGT) AMELIORATES THE PREECLAMPTIC PHENOTYPE IN RODENT MODELS OF PREECLAMPSIA

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Abstract

Investigational RNAI therapeutics for preeclampsia are highly potent mediators of gene-specific silencing. We tested angiotensinogen (AGT)-specific interfering RNA (siRNA) compounds (LUMI-AGT) for the ability to ameliorate symptoms of preeclampsia in established rat models, without inducing u-platelet pathology or affecting fetal health.

Background

Preeclampsia, a syndrome with the hallmark features of new-onset hypertension and proteinuria after 20 weeks of gestation, affects 5% of pregnancies in industrialized nations. It is a major cause of fetal and maternal morbidity/mortality. Several genetic studies have demonstrated that dysregulation of Angiotensin II (Ang) is involved in the pathogenesis of the disease; however, treatment with ACE inhibitor or AT1 receptor blocker is contraindicated due to fetal toxicity.

Methods

Two animal models of preeclampsia were used, which reflect different mechanisms inducing the preeclamptic phenotype in rodents. The first model (transgenic) acts by upregulation of the circulating and uteroplacental Bone-Angeotensin System (RUPP). The second model is a surgical model that induces ischemia/reperfusion injury and subsequent local and systemic inflammation restriction (RUPP). Beginning on day 3 of gestation, transgenic rats were dosed subcutaneously with 10 mg/kg siRNA every third day through gestation day 15. In RUPP rats, siRNA was subcutaneously injected once (1mg/kg) on day 12 of gestation.

Conclusion

These data demonstrate that an RNAI therapeutic targeting maternal hepatic AGT ameliorated the clinical sequelae of preeclampsia in rodent models of preeclampsia and improved the outcome of the fetus. This potential treatment strategy may offer selective drug delivery to the pregnant mother with no detectable delivery to the fetus.