**INTRODUCTION**

Galactosemia is a potentially life-threatening autosomal recessive metabolic disorder, affecting between 1/30,000-1/60,000 live births, that leads to neonatal, developmental, and adult changes in various tissues presumably resulting from the abnormal accumulation of toxic metabolites in the central nervous system, the lens of the eye, liver, kidney and other tissues.

- Affected infants are born seemingly healthy, but then experience a rapid and devastating decline following exposure to breast milk or milk formula, which contain large quantities of lactose, which is metabolized to galactose

- Acute symptoms can progress in a matter of days from jaundice, vomiting, and diarrhea to failure to thrive, hepatic, renal, and cerebral abnormalities, and E. coli sepsis. Without rapid dietary restriction of galactose, affected infants often die in the neonatal period.

- Despite dietary restriction of galactose, patients with galactosemia can experience severe phenotypes which include cognitive disability, speech delays, feeding difficulties, and diarrhea to failure to thrive, hepatomegaly, and developmental and functional decline following exposure to breast milk or milk formula.

- Affected tissues presumably result from the abnormal accumulation of toxic metabolites which leads to neonatal, developmental and adult changes in various tissues. (Figure 1)

AT is a unique candidate for treatment of galactosemia complications, since it acts on the polyol pathway, not the glycolytic pathway, that is activated in galactosemia.

**STUDY OBJECTIVES**

- The aim of this study was to assess the impact of treatment with AT-007, an Aldose Reductase Inhibitor, on formation of cataracts and metabolite levels (galactose & galactitol) in liver, brain and plasma in an animal model of galactosemia (GALT null rat)

- Genetic model: GALT null rats were homozygous for a frameshift (M3) mutation in the rat GALT gene. Wild-Type (WT), +/1, and heterozygous rats (+/M3) exhibited high levels of galactose, whereas M/M homozygotes (M/M3) did not express detectable GALT activity and showed abnormally high levels of galactitol, lactulose, and galactose in their plasma.

- Pup GALT genotypes (M1/M3, M2/M3, and M1/M2) were determined by DNA analysis using PCR, and plasma levels were quantified using HPLC.

- Treatment: Animal treatment began on the day after birth (neonatal Day 1), with the day of birth being designated Day 0. Animals were treated with either placebo (vehicle) or drug (AT-007) for 10 or 22 consecutive days and then euthanized on Day 10 or Day 22.

- Vehicle used to administer the drug to newborn pups was 0.5% Carbowax 4000.

- GALT null: Wild-type (WT), +/1, and heterozygous rats (+/M3) exhibited high levels of GALT activity, whereas M/M homozygotes (M/M3) did not express detectable GALT activity and showed abnormally high levels of galactitol, lactulose, and galactose in their plasma.

**METHODS**

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**RESULTS**

- Treatment with AT-007 led to significant reductions in galactitol in the GALT null rat in all tested tissues, including liver, brain and plasma.

- AT-007 treatment did not have a significant effect on galactose or Gal1P in this model.

- AT-007 completely prevented cataract formation in the GALT null rat, which uniformly developed severe cataracts when untreated.

**CONCLUSIONS**

- Galactosemia is an autosomal recessive disease that can be fatal in newborns and is associated with long-term complications, including cataracts, CNS related abnormalities, low bone density and primary ovarian insufficiency.

- While dietary restriction of lactose and galactose limits exogenous intake of galactose and prevents fatalities in infancy, it does not address the consequences of endogenous production of galactose, which significantly impacts development in children, and quality of life in adulthood.

- AT-007 (a novel ARI) effectively reduced galactitol levels in the GALT null rat model of classic galactosemia across relevant tissues, and prevented development of pre-senile cataracts in this model.

- This study confirms that the hypoglyceremic activity that is responsible for cataract formation in GALT deficiency, and treatment with an ARI can prevent formation of cataracts. Studies are ongoing to determine whether other long-term complications, such as CNS deficiencies, may be caused by elevated galactitol, and if treatment with AT-007 can prevent other long-term complications. AT-007 represents a potentially important new strategy for prevention and treatment of galactosemia complications.