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Enzyme Replacement Therapy With Investigational rhGUS (UX003) in an Infant With Non-immune Hydrops Fetalis (NIHF) and Mucopolysaccharidosis Type VII (MPS VII)

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ABSTRACT

Enzyme replacement therapy (ERT) early in life may reduce or prevent progression of many MPS disease manifestations. We report on 48 weeks of recombinant β-Glucouronidase (rhGUS, UX003) administration in an infant presenting with severe MPS VII.

A 30-week preterm male diagnosed prenatally with NIHF was born with anasarca, ascites, respiratory insufficiency requiring continuous non-invasive ventilation, and failure to thrive. At 4 months, a diagnosis of MPS VII was confirmed. His respiratory status deteriorated requiring tracheostomy and mechanical ventilation. Bronchoscopy revealed severe pharyngeal collapse, moderate tracheomalacia, severe bronchomalacia and deformities consistent with glycosaminoglycan (GAG) deposition. He experienced frequent episodes of severe desaturation with hypoxia and bradycardia, requiring resuscitation. Echocardiogram showed mild tricuspid insufficiency. Abdominal ultrasound revealed complex ascites and hepatomegaly. Neurologic exam revealed poor visual tracking, absent vocalizations, non-purposeful movements, truncal hypotonia and brisk reflexes.

At 5 months, an emergency IND was obtained for ERT with rhGUS at 2mg/kg biweekly. Urine GAGs showed a 70% reduction by week 24 and ascites and anasarca had resolved but his pulmonary status remained critical.

At 10 months, the dose of UX003-rhGUS was increased to 4 mg/kg biweekly and urine GAG decreased further to 90% reduction from baseline. At 17 months (48 week treatment) he demonstrated some improvement in pulmonary status. Neurologic exam was notable for visual tracking, sound recognition, social smile, cooing, grasping and transferring objects. Echocardiogram revealed mild mitral regurgitation. Abdominal ultrasound showed stable liver size and resolution of ascites and anasarca. No infusion associated reactions have occurred.

This first report of rhGUS ERT in an infant with MPS VII and NIHF showed significant reduction in urinary GAG and improvement in respiratory function, ascites, and neurological development. Long term follow up will determine whether there is further respiratory improvement and prevention of other systemic manifestations of MPS VII.

INTRODUCTION

- Mucopolysaccharidosis Type VII (Sly Syndrome, MPS VII) is an ultra-rare lysosomal storage disorder characterized by the deficiency of the enzyme β-glucuronidase (GUS).
- GUS is involved in the degradation of glycosaminoglycans (GAGs): chondroitin sulfate (CS), dermatan sulfate (DS) and heparan sulfate (HS).
- GUS deficiency leads to deposition of GAGs in lysosomes and subsequent dysfunction in multiple organ systems.
- The MPS VII phenotype ranges in severity and may present in its most severe form prenatally as non-immune hydrops fetalis (NIHF), characterized by ascites, anasarca, pleural effusions, and is often fatal, in addition to other systemic dysfunction.
- Milder forms may present at birth or within first few years of life with coarse facial features, hepatosplenomegaly, umbilical hernia, recurrent respiratory infections, dysostosis multiplex and a range of developmental delay.
- UX003, recombinant human GUS (rhGUS), is an investigational enzyme replacement therapy (ERT) in development for the treatment of MPS VII.
- In clinical studies, UX003 has been shown to reduce urinary GAG excretion (uGAG) and liver size in children ≥5 years and adults with MPS VII.
- Here we describe the first report of ERT with UX003 in a 4.5 month old infant with a severe form of MPS VII.

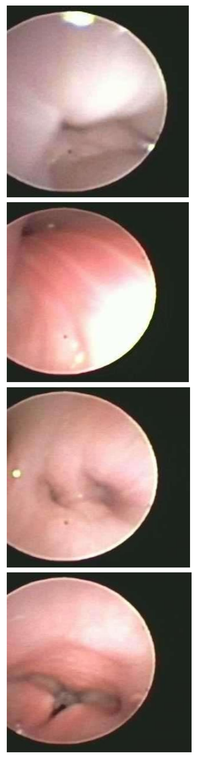
CASE DESCRIPTION

- 4.5-month-old baby boy born in March 2014 preterm at 30 6/7 week gestation complicated by prenatal diagnosis of fetal hydrops and unilateral ventriculomegaly
- Macrocephaly and developmental delay
- Anasarca with difficulty with fluid/electrolyte management
- Respiratory distress initially requiring non-invasive ventilation (CPAP)
- Feeding difficulty requiring placement of gastrostomy tube
- Mild hepatosplenomegaly
- ECHO at birth revealed patent ductus arteriosus (PDA); later ECHO showed mildly abnormal mitral valve
- MPS VII diagnosis in July 2014 confirmed by leukocyte lysosomal enzyme panel showing zero GUS activity

CLINICAL COURSE PRETREATMENT

- Respiratory status deteriorated
  - Episodes of oxygen desaturations with and without bradycardia
  - Required increasing pressures for his non-invasive ventilation (CPAP)
  - Bronchoscopy, revealed severe pharyngeal collapse, moderate tracheomalacia, severe bronchomalacia and deformities consistent with glycosaminoglycan (GAG) deposition (Figure 1)
  - Placement of tracheostomy tube
- Patient continued to experience frequent episodes of severe desaturation with hypoxia and bradycardia, requiring resuscitation and sedation to prevent agitation from precipitating further episodes.
- Baseline echocardiogram showed mild tricuspid insufficiency.
- Pretreatment abdominal MRI revealed complex ascites, hepatomegaly, 12 mm T2 hyperintense enhancing liver (See Fig 2).
- Neurologic exam revealed poor visual tracking, absent vocalizations, non-purposeful movements, truncal hypotonia and brisk reflexes.

Figure 1. Pretreatment Bronchoscopy



A. Pharyngeal Collapse

B. Severe deformity and expiratory collapse of right upper lobe

C. Severe deformity and collapse of right lower basal segments

D. Diffuse thickening of bronchial mucosa

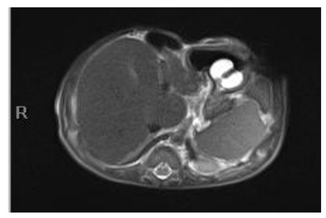


Figure 2. Pre-treatment. Abdominal MRI hepatomegaly with calculated liver volume of 237 cc (1.9 MN)

TREATMENT

Clinical Course on UX003 Treatment

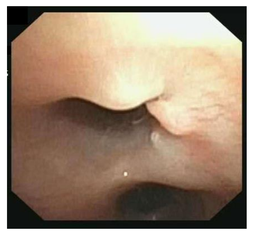
- Emergency IND was obtained for ERT with UX003 at 2 mg/kg biweekly
- Treatment started in September 2014 at 5 months of age with consent of parents
- By Week 4, Urine GAG decreased by 75% from baseline at 2 mg/kg dose (Table 1)
- At Week 18, UX003 dose increased to 4 mg/kg
- By Week 30, Urine GAG decreased further to 90% of baseline (Table 1)
- By Week 48 of treatment (17 months of age) he demonstrated some improvement in pulmonary status
  - Persistent moderate tracheomalacia and severe bronchomalacia
  - Weaned off sedatives and paralytics
  - Decreased frequency of hypoxic episodes ranging from days to weeks (maximum 21 days without an oxygen desaturation episode).
- Week 48 neurologic exam was notable for persistent truncal hypotonia, visual tracking, sound recognition, social smile, cooing, grasping and transferring objects.
- Week 48 ECHO revealed mild mitral regurgitation and stable trivial tricuspid insufficiency.
- Week 48 abdominal MRI showed stable liver size and resolution of ascites and anasarca.

Table 1. Urinary Glycosaminoglycans (uGAG) Reduced With UX003 Treatment

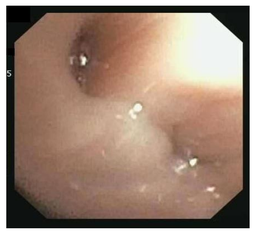
Collection Date	Visit	Chondroitin/ Dermatan Sulfate (mg/mmol creatinine) By NRE method	% of baseline uGAG (average of baseline 1 and baseline 2 = 31.5mg/mmol creatinine)
27-Aug-14	Baseline 1	38	-
2-Sep-14	Baseline 2	25	-
16-Sep-14	Week 2	16	51%
30-Sep-14	Week 4	8.2	26%
14-Oct-14	Week 6	7.5	24%
31-Oct-14	Week 8	6.9	22%
18-Nov-14	Week 10	7.3	23%
2-Dec-14	Week 12	6.9	22%
13-Jan-15*	Week 18	7.5	24%
24-Feb-15	Week 24	5.4	17%
19-May-15	Week 36	3.8	12%
11-Aug-15	Week 48	2.4	8%

*UX003 dose was increased from 2mg/kg to 4mg/kg on January 13, 2015

Figure 3: Week 23: Bronchoscopy

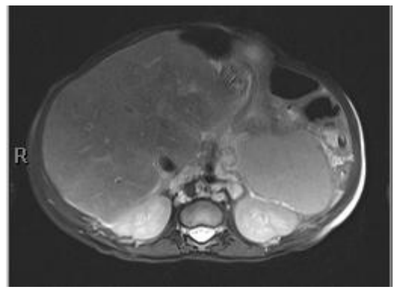


A. Left mainstem bronchus origin - extra tissue, which may represent either deposit in the bronchial wall or suction trauma



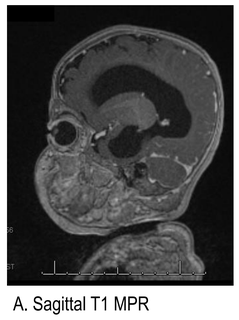
B. Right lower lobe - deformed and collapsed bronchi

Figure 4. Week 40: Abdominal MRI.

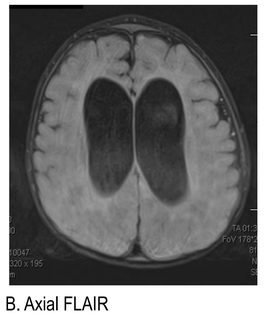


Mild Hepatomegaly with calculated liver volume of 436 cc (1.9 MN). Mild periportal edema. Resolution of liver lesion.

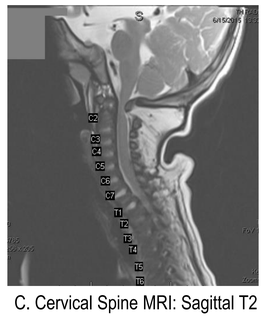
Figure 5. Week 40: MRI brain and Cervical Spine: Ventriculomegaly (A, B); and Severe spinal canal stenosis and cord compression at C1-C2 (C).



A. Sagittal T1 MPR



B. Axial FLAIR



C. Cervical Spine MRI: Sagittal T2

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SAFETY RESULTS

- No infusion associated reactions
- Six serious adverse events through Week 48 of treatment; none considered related to UX003 (Table 2)
  - Tension pneumothorax requiring thoracostomy tube placement
  - Cervical spine compression necessitating suboccipital craniectomy, C1 laminectomy at 15 months old
- No suspected unexpected serious adverse reactions (SUSARs) reported
- Adverse Events: none due to UX003
  - Recurrent tracheitis, requiring several courses of antibiotic therapy
  - Intermittent gastrostomy tube leaks requiring changes of the tube. Nutrition was adjusted when weight stagnated
  - Worsening ascites/Chylous ascites requiring therapeutic paracentesis at age 11 months
  - Positive fluid balance was treated with diuretics and his electrolytes abnormalities were stabilized as needed.
  - Ventriculomegaly without obstructive hydrocephalus, did not require intervention at 15 months

Table 2. SAEs During the Study

Summary of Serious Adverse Events Though Week 48		
Body System	**Serious Adverse Event Term**	**Relationship to UX003**
Cardiovascular	Bradycardia	Definitely not related
Respiratory	Apnea	Definitely not related
Respiratory	Hypoxia	Definitely not related
Respiratory	Tension Pneumothorax	Definitely not related
Nervous system	Cervical spinal cord compression	Definitely not related
Respiratory	Critical tracheal stenosis	Definitely not related

SUMMARY AND CONCLUSIONS

- After 48 weeks of UX003 treatment beginning at 5 months old in an infant with severe MPS VII, there was significant reduction in uGAG, ascites/ansarca resolved, developmental progress, persistent severe respiratory insufficiency with reduction in frequency of hypoxic episodes.
- There were no treatment-related adverse events.
- Earlier intervention in MPS VII may be needed to mitigate risk of irreversible damage as well as to prevent progression of this systemic disease.