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

Lau HA¹, Parmar S¹, Kazachkov M², Shah R², Wells J¹, Yachelevich N², Chopra A², Haller C¹, Kakkus E³
¹Department of Neurology, NYU Langone Medical Center, ²Department of Pediatrics, NYU Langone Medical Center, ³Ultragenyx

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-glucuronidase (rHGS, 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 hypoaxia and bradyaxida, 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 rhHGS at 2 mg/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-rHGS 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 hernias, recurrent respiratory infections, dysostosis multiplex and a range of developmental delay.

UX003, recombinant human GUS (rHGS), 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 (mg/mmol creatinine) and improvement in respiratory function, ascites, and neurological development of multiple organ systems.

CLINICAL COURSE ON UX003 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
- Six serious adverse events through Week 48 of treatment; none considered related to UX003
- Treatment started in September 2014 at 5 months of age with consent of parents
- Week 48 ECHO revealed mild mitral regurgitation and stable trivial 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.

By Week 48 of treatment (17 months of age) he demonstrated some improvement in respiratory status.

Mild Hepatomegaly with calculated liver volume of 436 cc (1.9 MN) with ultrasound

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/anasarca 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.

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

<table>
<thead>
<tr>
<th>Collection Date</th>
<th>Visit</th>
<th>Chondroitin/ Dermatan Sulfate (mg/mmol Creatinine)</th>
<th>% of baseline uGAG (average of baseline 1 and baseline 2 31.5 mg/mmol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-Aug-14</td>
<td>Baseline 1</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Baseline 2</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>16-Sep-14</td>
<td>Week 2</td>
<td>16</td>
<td>51%</td>
</tr>
<tr>
<td>30-Sep-4</td>
<td>Week 4</td>
<td>8.2</td>
<td>26%</td>
</tr>
<tr>
<td>14-Oct-14</td>
<td>Week 6</td>
<td>7.5</td>
<td>24%</td>
</tr>
<tr>
<td>31-Oct-14</td>
<td>Week 8</td>
<td>6.9</td>
<td>22%</td>
</tr>
<tr>
<td>18-Nov-14</td>
<td>Week 10</td>
<td>7.3</td>
<td>23%</td>
</tr>
<tr>
<td>2-Dec-14</td>
<td>Week 12</td>
<td>6.9</td>
<td>22%</td>
</tr>
<tr>
<td>13-Jan-15²</td>
<td>Week 18</td>
<td>7.5</td>
<td>24%</td>
</tr>
<tr>
<td>24-Feb-15</td>
<td>Week 24</td>
<td>5.4</td>
<td>17%</td>
</tr>
<tr>
<td>19-May-15</td>
<td>Week 36</td>
<td>3.8</td>
<td>12%</td>
</tr>
<tr>
<td>11-Aug-15</td>
<td>Week 48</td>
<td>2.4</td>
<td>8%</td>
</tr>
</tbody>
</table>

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

REFERENCES


SAFETY RESULTS

Table 2. SAEs During the Study

<table>
<thead>
<tr>
<th>Body System</th>
<th>Serious Adverse Event Term</th>
<th>Relationship to UX003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Bradycardia</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Apnea</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Hypoxia</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tension Pneumothorax</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Cervical spinal cord compression</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Critical tracheal stenosis</td>
<td>Definitely not related</td>
</tr>
</tbody>
</table>

Figure 1. Pretreatment Bronchoscopy
A. Pharyngeal Collapse
B. Severe deformity and esophageal collapse at 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)

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 portal 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