Evidence of Early Bone Response After Initiation of ERT in a 3-Year Old Patient With MPS VII

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ABSTRACT

Skeletal involvement is a common feature in the mucopolysaccharidoses (MPS) and includes short stature, dysostosis multiplex, joint pain, stiffness and/or laxity. Early enzyme replacement therapy (ERT) in the first few years of life may reduce or prevent MPS bone disease manifestations. Potential skeletal benefits of early intervention in MPS VII have not been described. We report an early marked response in bone biomarkers in a young child after a single IV dose of rhGUS (UX003), which is under development as a potential ERT for MPS VII.

A 3-year-old male with MPS VII characterized by short stature (< 3rd height for age) participating in an open-label trial of rhGUS 4 mg/kg biweekly in patients < 5 years had a normal baseline alkaline phosphatase (ALP) of 186 U/L which rose significantly to 1633 U/L (reference range 104-345) two weeks after the first infusion. Bone-specific ALP was mildly elevated at 111 U/L (reference range 31-103), and Procollagen Type 1 N-terminal propeptide (P1NP) was significantly increased at 470 mcg/L (reference range 22-150) indicative of robust bone formation. A marker of bone resorption, C-telopeptide (CTX) was within normal limits. The patient was asymptomatic with no recent illnesses, injuries or fractures. Other laboratory values including liver and thyroid function tests were unremarkable.

In MPS glycosaminoglycans accumulate in the lysosomes of cells including osteoblasts, which disrupt the normal cycle of bone formation and remodeling leading to structurally and functionally abnormal bone.

In this young child with MPS VII, a marked increase in bone turnover markers, P1NP and ALP was observed after a single IV dose of rhGUS. Although preliminary, this observation suggests replacement of β-glucuronidase early in life may activate the normal bone growth cycle and potentially reduce the long term skeletal manifestations of the disease. Additional bone biomarker data may further inform this observation.

PATIENT GROWTH CHART

Table 1. Bone Biomarkers for 3 yo MPS VII Patient in Clinical Trial of rhGUS

<table>
<thead>
<tr>
<th>Study Week</th>
<th>ALP (U/L) Ref range 104-345</th>
<th>BALP (U/L)* Ref range 31-103</th>
<th>P1NP (mcg/L) Ref range 22-150</th>
<th>CTX (pg/mL) Ref Range 1500-1700</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>196</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Baseline*</td>
<td>139</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Week 2</td>
<td>1633</td>
<td>-----</td>
<td>470</td>
<td>822</td>
</tr>
<tr>
<td>Week 4</td>
<td>402</td>
<td>111</td>
<td>470</td>
<td>822</td>
</tr>
<tr>
<td>Week 8</td>
<td>185</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Week 16</td>
<td>181</td>
<td>47.3</td>
<td>410</td>
<td>788</td>
</tr>
</tbody>
</table>

Abbreviations: ALP = alkaline phosphatase; BALP = bone-specific alkaline phosphatase; CTX = C-terminal telopeptide; P1NP = Procollagen Type 1 N-terminal propeptide; *BALP measured by Quantitative Chemiluminescent Immunoassay; Baseline measurement taken before first infusion.

SUMMARY

- Alkaline Phosphatase (ALP)
  - ALP levels were normal at Baseline and increased by more than 4-fold the upper limit of the reference range by Week 2 after initiating UX003 therapy
  - ALP levels remained slightly elevated at Week 4 and then decreased to screening levels by Week 8

- Bone specific ALP (BALP) and Procollagen type 1 N-terminal propeptide (P1NP) are bone formation markers
  - At Week 4, BALP and P1NP were elevated indicating increased bone formation
  - At Week 16, BALP levels had returned to the reference range but P1NP remained substantially elevated

- C-Telopeptide (CTX) is a bone resorption biomarker
  - CTX levels were within normal limits for healthy children (Herrmann et al. 2014) suggesting bone resorption was not increased by rhGUS therapy

CONCLUSIONS

- These early data in a single MPS VII pre-pubertal patient treated with rhGUS provide preliminary evidence that enzyme replacement therapy may stimulate bone formation.
  - Based on historical studies in MPS animal models, the early initiation of enzyme replacement therapy can improve bone morphology consistent with the observed effect of rhGUS on bone turnover markers in this young patient (Sands et al 1994, Byers et al 1997).
  - Bone formation biomarkers will be explored in other prepubertal patients with MPS VII in addition to monitoring growth while on long term treatment with rhGUS.

REFERENCES


PHYSIOLOGY OF BONE REMODELING