**INTRODUCTION**

- Renal osteodystrophy is an integral component of chronic kidney disease-mineral/bone disorder (CKD-MBD). CKD-MBD is strongly associated with unacceptable morbidity and mortality in end-stage kidney disease (ESKD).
- Activin A is a transforming growth factor-ß superfamily protein that is found at high levels in bone: its signaling is through the type II activin A receptor (ActRIIA).
- Inhibins, an inhibitor of activin A signaling, is produced in the ovaries and stimulates bone growth.1,2
- Decreased inhibin expression is associated with post-menopausal bone loss.1,2

- Non-clinical studies suggest that RAP-011 (the murine ActRIIA-IgG1 antibody) analog to the human activin-A/ActRIIA NGF analog to the human activin-A receptor) modulates the balance between bone formation and bone resorption activity by blocking signaling through ActRIIA.2,3
- A mouse model of abdominal aortic aneurysm (AAA) and 6/6 reperfused recapitulates many aspects of CKD-MBD, including vascular calcification, hypertension, hyperphosphatemia, elevated FGF-23, and hyperparathyroidism.2,3
- Despite hyperparathyroidism, loss of bone mass is associated with adynamic bone disease assessed by histomorphometry in the CKD mice.4
- In the dd/y→high-fat fed: 5/6 nephrectomy model of vascular calcification, RAP-011 inhibited Smad-dependent signaling, blocked aortic calcification, increased vascular smooth muscle protein expression, and decreased CKD-stimulated vascular calcification.5
- The goal of this study was to evaluate the role of activin signaling in the pathogenesis of renal osteodystrophy.

**METHODS**

- The 4 different groups of mice used in this study are described in Table 1.
- Sham-operated idr+/−→high-fat fed mice (n=12) and high-fat fed mice (n=12) were fed a high-fat diet to induce hypercholesterolemia and hypertriglyceridemia. C57BL/6 mice on a high-fat diet (HFD) or sham (n=7; n=7) were used as controls for the histomorphometry results for C57-BL/6 mice were compared with wild type (WT) mice (n=5) and sham (n=12).

**RESULTS**

- Action A levels were increased in a model of CKD (Figure 1), making the use of RAP-011 as an activin inhibitor a viable therapeutic approach.2,6
- Kidney function was reduced to a degree that is analogous to human stage 3 CKD (CKD-3) in the 2 groups of idr+/−→ablatable C57-BL/6 mice studied.

**Figure 1. CKD Increases Activin A in the Circulation**

**Table 1. Groups of Mice Used in the Idr+/−→High-Fat Fed Mouse Model**

<table>
<thead>
<tr>
<th>Groups of Mice</th>
<th>Allocation/Weight</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type (C57BL/6 J)</td>
<td>50 g, male (n=5)</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>idr+/−→high-fat fed, sham-operated</td>
<td>50 g, male (n=7)</td>
<td>13</td>
</tr>
<tr>
<td>idr+/−→high-fat fed, 5/6 nephrectomy, vehicle-treated for 22 weeks to 28</td>
<td>50 g, male (n=7)</td>
<td>13</td>
</tr>
<tr>
<td>idr+/−→high-fat fed, 5/6 nephrectomy, RAP-011 treatment for 22 weeks to 28</td>
<td>50 g, male (n=7)</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 2. Histomorphometric Results (Mean±SEM)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Osteoid formation rate/osteoblast surface, %</th>
<th>Mineralizing surface/bone surface, %</th>
<th>Osteoid mineralization lag time, days</th>
<th>Erosion surface/bone surface, %</th>
<th>Osteoid thickness, µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
</tr>
<tr>
<td>Sham</td>
<td>1.05±0.10</td>
<td>1.05±0.10</td>
<td>1.05±0.10</td>
<td>1.05±0.10</td>
<td>1.05±0.10</td>
</tr>
<tr>
<td>CKD-3 V</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
</tr>
<tr>
<td>CKD-3 R</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
<td>0.68±0.08</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- Increased circulating activin contributes to the high turnover osteodystrophy associated with CKD-3 mice.
- Action A inhibition with RAP-011, an Activin A receptor inhibitor, increased BV in CKD-3 by inhibiting bone resorption and bone formation rate/erosion, countervailing the negative effects of CKD.

**REFERENCES**


This study was sponsored by Celgene Corporation and Kentucky Nephrology Research Trust. Presented at: the 52nd ERA-EDTA Congress; May 28–31, 2010; London, UK.