Increased Cancellous Bone Connectivity and Conserved Cortical Bone Mass in PTH[1-34] (LY333334)-Treated Monkeys

C. Jerome¹, T. Gladwell¹, K. Scheer¹, R. Brommage², J. Hock³

¹SkeleTech, Inc., Kirkland, WA
²Wake Forest University School of Medicine, Winston-Salem, NC
and
²Lilly Research Laboratories, Indianapolis, IN

XXVIth European Symposium on Calcified Tissues
Maastricht, The Netherlands May 7-11, 1999
### Experimental Design

- Skeletally mature, female cynomolgus monkeys randomized to 6 treatments, 19-20 animals per group

### Treatment Groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Dose (µg/kg/day)</th>
<th>Treatment (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LY333334</td>
</tr>
<tr>
<td>S</td>
<td>Sham/Vehicle</td>
<td>—</td>
</tr>
<tr>
<td>O</td>
<td>OVX/Vehicle</td>
<td>—</td>
</tr>
<tr>
<td>L</td>
<td>OVX/LY3334</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>OVX/LY3334</td>
<td>5</td>
</tr>
<tr>
<td>LW</td>
<td>OVX/LY3334</td>
<td>1</td>
</tr>
<tr>
<td>HW</td>
<td>OVX/LY3334</td>
<td>5</td>
</tr>
</tbody>
</table>
Bone Histomorphometry

- Animals were labeled with calcein prior to necropsy

Samples

- Undecalcified
  - 5-10 µm transverse sections
  - Lumbar vertebral body (LV), femur neck (FN), and distal radius (DR)

- Undecalcified
  - 100 µm transverse sections
  - Mid-shaft radius (MR) and mid-shaft femur (MF)

- OsteoMeasure™ system used to analyze central cancellous bone in LV, FN, and DR and for the entire sections of MR and MF

- Derived variables included bone structure indices (BV/TV, Tb.Th, Tb.N, and Tb.Sp) and dynamic indices of bone formation (BFR/BV)

Data were subjected to ANOVA (SAS Proc Mixed). The Bonferroni correction was used for evaluation of multiple comparisons at p< 0.05
Trabecular Bone

Distal Radius  Femoral Neck  Vertebra
Cortical Bone

Radius Midshaft

Midshaft Femur
Cancellous Bone Volume

![Bar chart showing BV/TV (%) for different regions: DR, LV, and FN. The chart compares S, O, L, H, LW, and HW categories, with significance indicated by asterisks.](image-url)
Trabecular Thickness

Tb.Th (um)

DR  LV  FN

S  O  L  H  LW  HW
Trabecular Number

Tb.N (mm\(^{-1}\))

- DR
- LV
- FN

Legend:
- S
- O
- L
- H
- LW
- HW
Tunneling
# Tunneling Data

<table>
<thead>
<tr>
<th>Trabecular Tunneling Score</th>
<th>% of Treatment Group at Each Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>+</td>
<td>16</td>
</tr>
<tr>
<td>++</td>
<td>26</td>
</tr>
<tr>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>
Diaphyseal Bone Area

B.Ar (mm^2)

MR

MF

S
O
L
H
LW
HW
Midshaft Radius Intramedullary Bone
Midshaft Femur Intramedullary Bone
Cancellous Bone Formation

BFR/BV (%) vs. DR, LV, FN

S, O, L, H, LW, HW
Total Diaphyseal Bone Formation Rate

![Bar chart showing Total Diaphyseal Bone Formation Rate (%)]

- S: Light green
- O: Light yellow
- L: Light blue
- H: Light grey
- LW: Light brown
- HW: Light orange

* Denotes statistically significant difference
Summary

- LY333334-treated animals had increased cancellous bone volume due to increased trabecular number and reduced separation.

- Longitudinal tunneling of thickened trabeculae appeared to be the mechanism for these structural changes.

- Bone volume remained elevated but tunneling was eliminated 6 months after withdrawal of treatment.

- LY333334-treated animals had increased cortical porosity associated with increased bone formation rates, but total cortical bone mass was conserved.

- Increased porosity was at least partially reversed upon withdrawal of treatment for 6 months.
Conclusions

- LY333334 increases cancellous bone mass at axial and appendicular sites by a mechanism that increases connectivity measures.
- LY333334 causes increased diaphyseal porosity associated with high bone turnover rates (increased remodeling space).
- Cancellous bone gains remain after withdrawal of LY333334 treatment.
- Cortical porosity is at least partially reversible upon withdrawal of LY333334 treatment.

*LY333334 treatment causes dramatic increases in cancellous bone mass without significantly compromising cortical bone. These findings in an animal model, with similar skeletal structure and function to the human, support the use of LY333334 for prevention and treatment of osteoporosis.*