Treatment with eldecalcitol (ED-71) and raloxifene combined increases cancellous and cortical bone strength in ovariectomized rats.

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Backgrounds

- Eldecalcitol (ED-71; ELD), a 2β-hydroxypropyloxy derivative of 1α,25(OH)$_2$D$_3$, was approved for treatment of osteoporosis in Japan in 2011.
- ELD significantly reduced the incidence of vertebral and wrist fractures compared with alfacalcidol, a prodrug of 1α,25(OH)$_2$D$_3$, in a 3-year clinical study [1].
- ELD inhibited osteoclastic bone resorption and increased bone mass more potently than alfacalcidol in ovariectomized (OVX) rats [2].
- Raloxifene (RAL), a selective estrogen receptor modulator, is globally approved for the treatment and prevention of postmenopausal osteoporosis.
- There are no reports describing the efficacy of combination treatment of ELD with RAL in osteoporosis patients or in animal models.

[1] Matsumoto T et al. Bone 49: 605 (2011)
[2] Uchiyama Y et al. Bone 30: 582 (2002)

Objective

To compare the effects of combining ELD and RAL against each monotherapy in osteoporotic rats.

Summary

The combination treatment with ELD and RAL
- improved bone mechanical strength by suppressing bone turnover and increasing BMD more than either monotherapy
- reduced the rise of blood Ca and urinary Ca excretion seen in ELD monotherapy.
- may avoid excessive reduction of bone turnover.
- showed additive effect on inhibition of mouse bone marrow osteoclastogenesis.

Results

Fig. 1 Bone resorption marker

ELD + RAL significantly decreased urinary DPD compared with ELD (4 wks) or RAL (4, 8 and 12 wks) monotherapy.

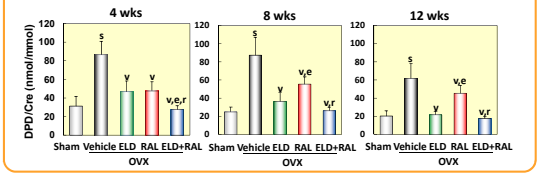


Fig. 2 Bone mineral density

ELD + RAL significantly increased BMD of lumbar spine and femur compared with either monotherapy.

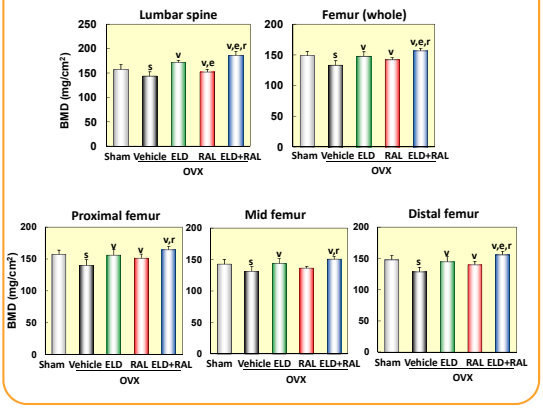


Fig. 3 Mechanical strength of lumbar vertebra (L5) and femoral midshaft

The combination treatment increased the mechanical strength of lumbar vertebra and femoral midshaft.

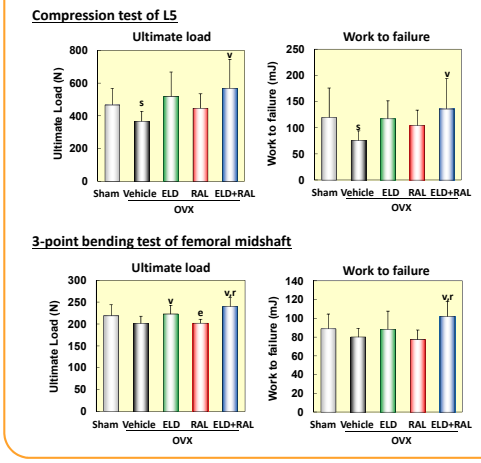


Table 1 Serum Ca and urinary Ca/Cre (12 wk)

ELD + RAL reduced the increase in serum Ca and urinary Ca/Cre by ELD.

	Sham	OVX Vehicle	OVX ELD	OVX RAL	OVX ELD+RAL
Serum Ca (mg/dL)	10.34 ± 0.31	9.92 ± 0.23 ^{s}	10.72 ± 0.36 ^{v}	9.62 ± 0.24 ^{e}	10.25 ± 0.34 ^{e,r}
Urinary Ca/Cre	0.037 ± 0.011	0.038 ± 0.011	0.346 ± 0.058 ^{v}	0.042 ± 0.054 ^{e}	0.198 ± 0.046 ^{v,e,r}

Mean + SD
$^{s}P < 0.05$ vs. sham by unpaired t-test.
$^{v}P < 0.05$ vs. OVX + vehicle, $^{e}P < 0.05$ vs. OVX + ELD, $^{r}P < 0.05$ vs. OVX + RAL by Tukey's multiple comparison test.

Fig. 4 Bone histomorphometry

ELD + RAL decreased the number of osteoclast compared with RAL monotherapy, and lowered bone formation parameters to sham control levels.

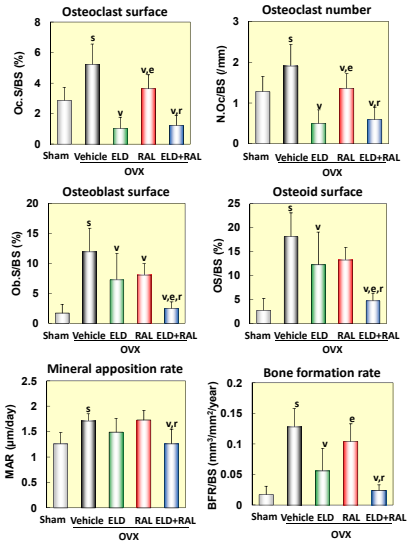
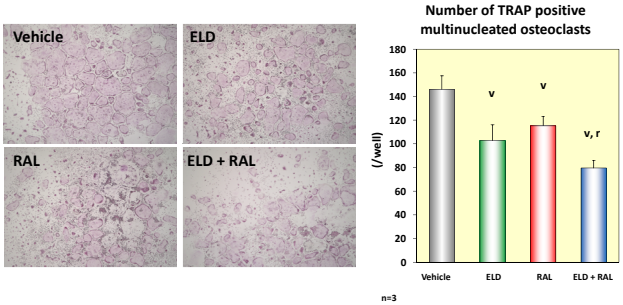


Fig. 5 *In vitro* osteoclastogenesis

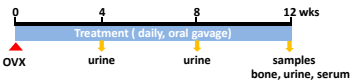
The combination treatment with ELD and RAL showed additive effect on inhibition of mouse bone marrow osteoclastogenesis.



n=3
v p<0.05 vs Vehicle by Tukey's multiple comparison test
r p<0.05 vs RAL by Tukey's multiple comparison test

Methods

In vivo



Animals: 8-month-old female Wistar-Imamichi rats
Treatment: Daily, 12 weeks, by oral gavage
Groups: (n = 10)
- Sham Vehicle
- OVX Vehicle
- OVX ELD 7.5 ng/kg
- OVX RAL 0.3 mg/kg
- OVX ELD 7.5 ng/kg + RAL 0.3 mg/kg

Measurements:
- Bone resorption marker: Urinary deoxypyridinoline (DPD)
- BMD: Lumbar spine (L2-L4), femur
- Bone biomechanical strength: Lumbar vertebral body (L5), femur
- Bone histomorphometry: Lumbar vertebral body (L3)
- Serum calcium (Ca), urinary Ca, urinary creatinine (Cre)

In vitro

Mouse Bone Marrow 30 ng/mL M-CSF
30 ng/mL RANKL

with or without
- 10^{-7}M ELD
- 10^{-6}M RAL
- 10^{-7}M ELD + 10^{-6}M RAL

Count a number of TRAP positive multinucleated osteoclast.

【COI】All authors are employees of Chugai Pharmaceutical Co., Ltd.