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

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Backgrounds

- Eldecalcitrol (ED-71; ELD), a 28-hydroxypropoxy derivative of 1α,25(OH)2D3, was approved for treatment of osteoporosis in Japan in 2011.
- ELD significantly reduced the incidence of vertebral and wrist fractures compared with alfalcacidol, a prodrug of 1α,25(OH)2D3, in a 3-year clinical study [1].
- ELD inhibited osteoclastic bone resorption and increased bone mass more potently than alfalcacidol 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.

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

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

Fig. 2 Bone mineral density

EDL + RAL significantly increased BMD of lumbar spine and femur 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.

Fig. 4 Bone histomorphometry

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

Table 1 Serum Ca and urinary Ca/Cr (12 wks)

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

Methods

Animals: 8-month-old female Wistar-Tsukishima rats
Treatment: Daily, 12 weeks, by oral gavage
Groups: (n = 10)
- Sham
- Vehicle
- OVX
- Vehicle
- OVX
- ELD 7.5 mg/kg
- OVX
- ELD 0.3 mg/kg
- OVX
- ELD 7.5 mg/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 (L5)
- Serum calcium (Ca), urinary Ca, urinary creatinine [Cre]

Fig. 5 In vitro osteoclastogenesis

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