Direct administration of zoledronate acid improves bone structure in local osteoporotic lesion of ovariectomized rats

YOHEI MATSUO, M. Kashii, T. Sugiura, M. Furuya, T. Morimoto, H. Honda, T. Kaito, M. Iwasaki, H. Yoshikawa
Dept. of Orthopedic Surgery, Osaka University Graduate School of Medicine, JAPAN

Correspondence to Yohei Matsuo, MD
Dept. of Orthopedic Surgery, Faculty of Medicine Graduate School of Medicine, Osaka University 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: ymatsuo197988@gmail.com

Introduction

- Management of local osteoporotic lesions is a clinical difficult problem, and intravenous administration of bisphosphonates (BPs) has a limited effect for local osteoporotic or osteolytic lesion.
- Zoledronate acid (ZOL) is the most potent BP that strongly inhibits osteoclast function with high binding affinities for bone.
- We hypothesized that direct administration of high-dose ZOL for local osteoporotic or osteolytic lesion enables to improve local bone structure without any systemic side effects.

Objectives

To examine the efficacy and safety of direct administration of ZOL on local osteoporotic lesion of ovariectomized rats

Materials & Methods

Animals

Rats Sprague Dawley (SD), **6 months-old, female** (SLC, Japan)

Regents

Zoledronate acid (ZOL) purchased from Novartis Pharmaceuticals Japan
Dose: **67μg/kg** equal to the recommended dose for human

Procedure of the local injection into the bone marrow

1) Check the joint line using the scout view of micro CT (Fig.1)
2) Make the two holes at the right proximal tibia (Fig.2)
3) Flash and open the route between the two holes (Fig.3)
4) Administer ZOL or saline into the bone marrow

Fig.1

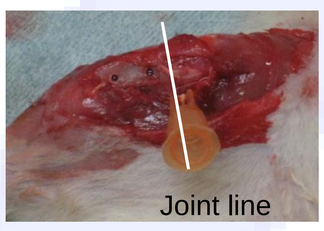


Fig.2

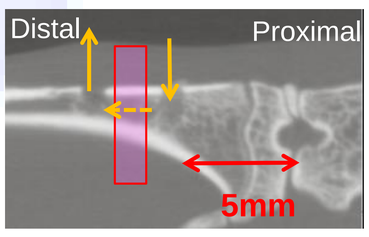
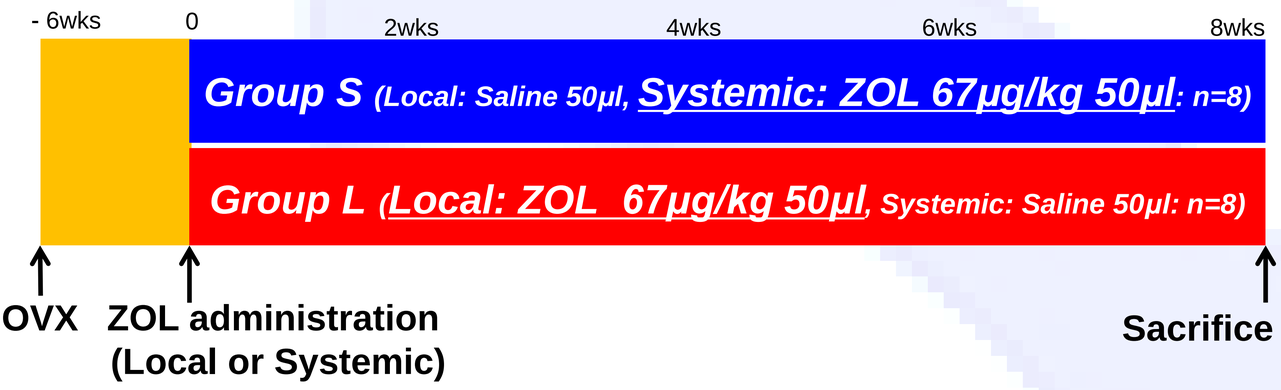


Fig.3

Experimental design

Ovariectomy (OVX) caused osteoporosis and deterioration of three-dimensional (3D) trabecular microstructure. Six weeks later after OVX, rats were divided into the two groups.



Assessment

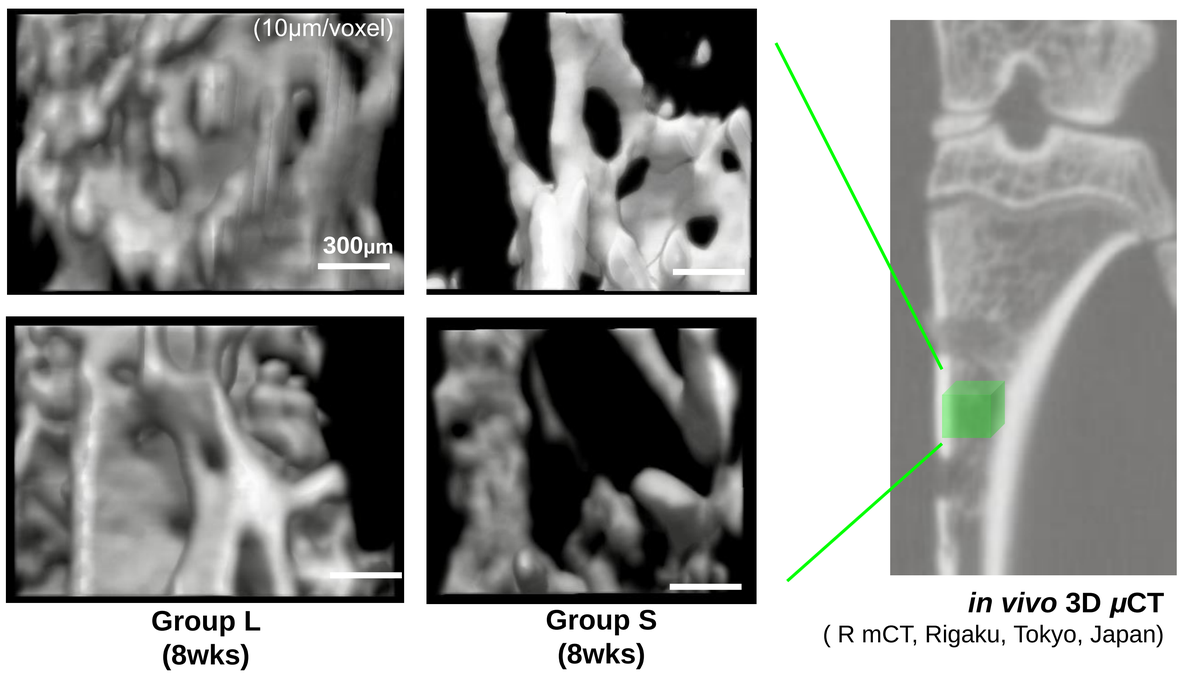
***In vivo* micro CT (μCT)**

- **Volumetric BMD measurements & 3D trabecular microstructural analysis**
- Measurement interval: **0, 2, 4, 6 and 8 weeks**
- Analyzed area: **local osteoporotic lesion**

Area 1: Cancellous bone area of the right tibia between the two holes (Fig.3)
Area 2: Mirror area of the left tibia

Results

Deleterious microstructure by OVX further improved in the group L



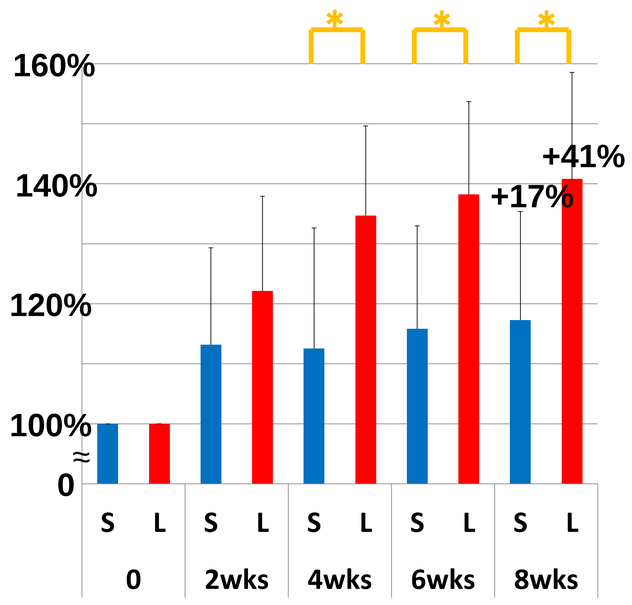
Group L (8wks)

Group S (8wks)

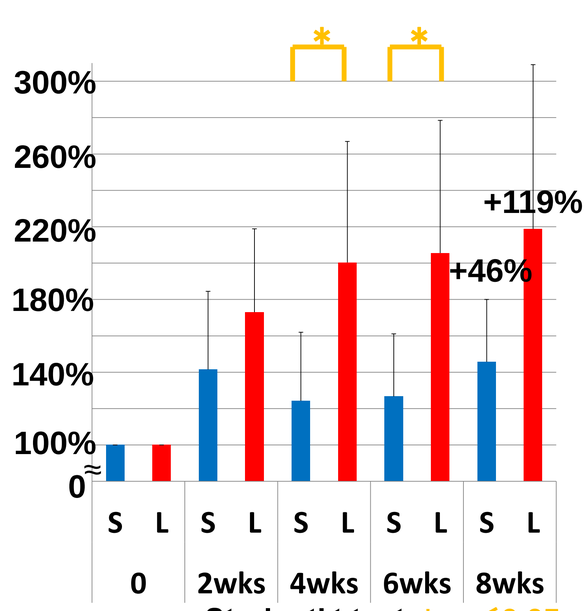
***in vivo* 3D μCT**
(R mCT, Rigaku, Tokyo, Japan)

BMD, BV/TV, and other microstructural parameters (Tb.Th BS/BV) significantly increased with time by local ZOL administration

Change of vBMD at Area1



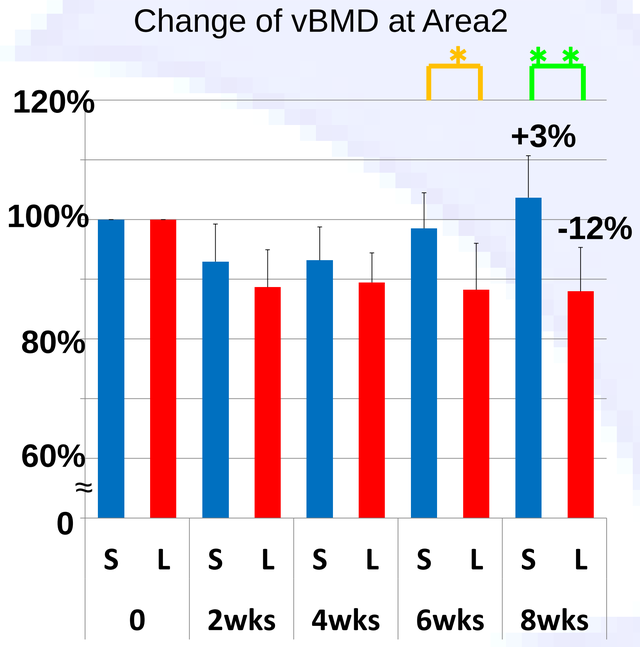
Change of BV/TV at Area1



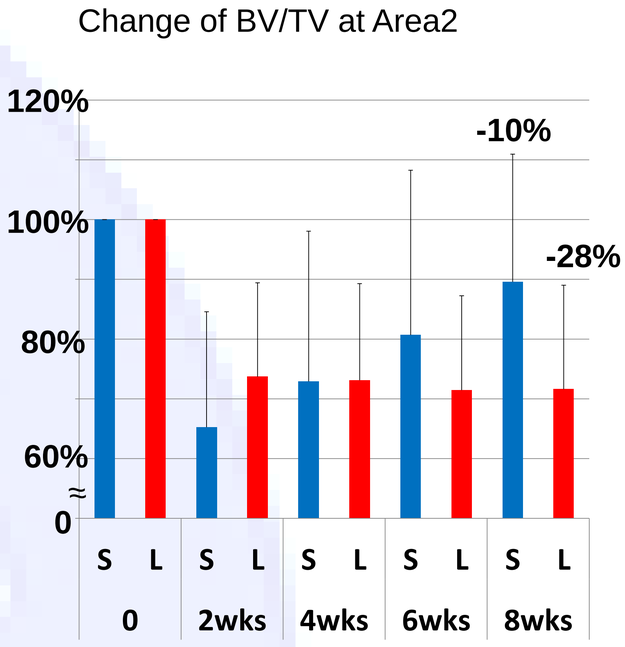
Student' t test *: p＜0.05

Systemic ZOL administration improved bone loss and deleterious microstructure by OVX, but local ZOL administration had little influence on other bone tissue.

Change of vBMD at Area2



Change of BV/TV at Area2



Student' t test *: p＜0.05, **p＜0.01

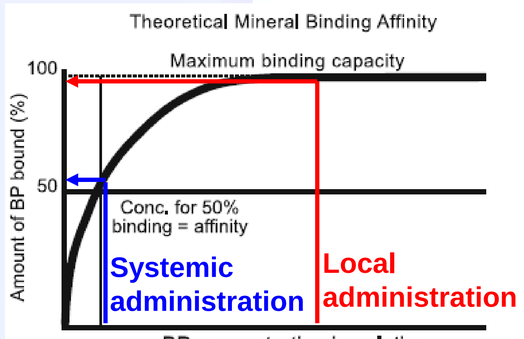
Discussions

There were a few reports that direct administration of ZOL accelerated fracture healing .But there is no report that direct administration of ZOL improves local osteoporotic lesion.

SH Greiner et al Acta Orthopaedica (2008)

Bisphosphonates are two key properties
① **High affinities for bone mineral** (ZOL > ALN > IBN > RIS)
② **Inhibitory effects on osteoclast** (ZOL > RIS IBN > ALN)

R.G.G.Russell et al Osteoporos Int (2008)



When BP concentration in solution is extremely high, 100% binding to hydroxyapatite is achieved in theory .

For local osteoporotic or osteolytic lesion, much higher concentration is achieved in local administration.

Local administration can inhibit the activity of osteoclast more strongly than systemic administration.

Future direction

Further analysis are on going and are planned.

1) Histological analysis of the local lesion (TRAP strain, bone histomorphometrical analysis)
2) Dose testing for local ZOL administration
3) Analysis of effects throughout the body
   Biochemical examination, histological examination for other bone tissues…

Conclusions

Direct administration of high-dose ZOL for local osteoporotic lesions have more beneficial effects on local bone structure than systemic administration, and have little influence on other bone tissue.

Disclosure

◆ This work was partially supported by the AO Foundation (Davos, Switzerland) and by the grants from AOSpine Japan.
◆ None of the authors has any financial interest with any of the commercial entities.
◆ All authors state that they have no conflicts of interest.