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Case Study

A Real-World Pilot Study on Zoledronate-based Treatment of Osteoporosis in Japanese Women Aged Over 65 years Including Very Advanced Age

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Abstract

Introduction: This study included 50 elderly Japanese women aged 65 years and older selected from 87 patients with osteoporosis treated with zoledronate infusion who were followed up for 1 year or longer across three participating institutions.

Subjects and Methods: The age of the study patients ranged from 65 to 95 years, and body mass index ranged from 14.6 to 29.0 kg/m^2. There were 23 women who had received one course of infusion and 27 who had received two courses or more. Surgery for bone fractures was performed prior to infusion in 20 women, and 30 women had no history of surgery.

Results: There was no significant correlation between age and body mass index (r = 0.07). The increase in femoral bone mineral density was negatively correlated with age (r = -0.50), but it tended to show a positive correlation with body mass index (r = 0.31).

Discussion: This study included very advanced aged and lean Japanese women, and despite its small sample size, it demonstrated that zoledronate infusion was less effective in increasing femoral bone mineral density in (1) women with a low body mass index, (2) those of a very advanced age, and (3) those with a history of surgery.

Conclusion: Zoledronate infusion can be reliably administered rapidly over 15 min once a year, and zoledronate is an effective drug for elderly and lean Japanese women as long as chronic kidney disease is considered.

Keywords: *Osteoporosis; Zoledronate; Advanced Age; Japanese Women; Body Mass Index*

Abbreviations

Zol: Zoledronate; BP: Bisphophonate; F-BMD: Femoral Bone Mineral Density; BMI: Body Mass Index; VD: Vitamin D; CKD: Chronic Kidney Disease; NTx: Cross-Linked N-terminal Telopeptides

Introduction

Zoledronic acid, or zoledronate, is a third-generation bisphosphonate (BP) first developed by Novartis [1]. It is known to suppress bone resorption by inhibiting osteoclastogenesis, resulting in a loss of function and apoptosis of osteoclasts. This drug is indicated in the treatment of osteoporosis in postmenopausal women, male patients, and those with steroid-induced osteoporosis as well as of hypercalcemia caused by malignant tumor, bone lesions in multiple myeloma and bone metastasis from solid cancer, and Paget's disease of bone [2]. In the case of osteoporosis, bone resorption markers can be suppressed for approximately 1 year by administering zoledronate at a

dose of 5 mg; no racial differences have been observed in terms of its efficacy to date [3]. Many elderly individuals currently live in Japan; thus, the continuation rate of osteoporosis treatment remains a major issue. Because outpatient treatment may be difficult for institutionalized patients, there is an increasing number of patients receiving annual zoledronate infusion (Zol: Reclast®, Asahi Kasei Medical Co., Ltd.), which is considered reliably effective. This study included 50 elderly women aged 65 years and older selected from 87 patients with osteoporosis treated with Zol infusion who were followed up for 1 year or longer across three participating institutions. We retrospectively evaluated the changes in femoral bone mineral density (F-BMD: measured at the femoral neck with a HOLOGIC densitometer) in association with factors such as age at infusion, body mass index (BMI), presence or absence of surgery for low-trauma fractures prior to infusion, and pretreatment procedures.

Subjects

The age of the study patients ranged from 65 to 95 years (mean, 79.1 ± 8.6 years) and BMI ranged from 14.6 to 29.0 kg/m^2 (mean, 20.6 ± 2.8 kg/m^2). There were 23 women who had received one course of infusion and 27 who had received two courses or more. Surgery for bone fractures (e.g. femoral, humeral, vertebral, and wrist fractures) was performed prior to infusion in 20 women, and 30 women had no history of surgery. Observed complications included periodontitis, kyphosis, osteoarthritis/spondylosis, hypertension, diabetes mellitus, and dementia. Various pretreatment procedures were used that ranged from vitamin D (VD) monotherapy to parathyroid hormone replacement. Regarding the level of care needed at the first infusion, 43 women were either house-, chair-, or bed-bound.

Results

Although zoledronate was replaced with an anti-receptor activator of nuclear factor kappa-B ligand antibody considering the measures against chronic kidney disease (CKD: estimated glomerular filtration rate < 40 - 60) in six women during the study period, F-BMD was ultimately increased by a mean of 2.5% (range, 0% - 6%). Notably, no woman required dialysis, and no serious complications were observed following Zol infusion. Further, there was no significant correlation between age and BMI (r = 0.07). The increase in F-BMD was negatively correlated with age (Figure 1, r = -0.50), but it tended to show a positive correlation with BMI (Figure 2, r = 0.31). The increase in F-BMD was 1.45 ± 3.93 in the surgery group and 3.32 ± 5.32 in the non-surgery group, indicating a larger increase in the latter. The proportion of patients showing an increase of 3% or more between before and after infusion was 7/20 (35%) in the surgery group and 16/30 (53%) in the non-surgery group. Moreover, the increase in F-BMD was 2.35 ± 5.29 in the one-course group and 2.81 ± 5.45 in the two-course group with no significant differences. During the study period, three women suffered a low-trauma fracture (a 77-year-old woman with a femoral neck fracture, a 78-year-old woman with a vertebral fracture, and an 84- year-old woman with a Colle's fracture, all had undergone a preceding surgery). Their F-BMD decreased on an average by 3% (range, 0% - 8%). Pretreatment procedures could not be compared owing to a substantial diversity and variation among the patients. To prevent acute-phase reactions, the first infusion was supplemented and pre-administered with acetaminophen/antihistamine. A 71-year-old woman (switching from VD + BP) exhibited a severe acute-phase reaction, requiring extension of infusion time. However, the continuation of infusion was possible. At the end of the study period, the level of care needed did not increase in any patient.

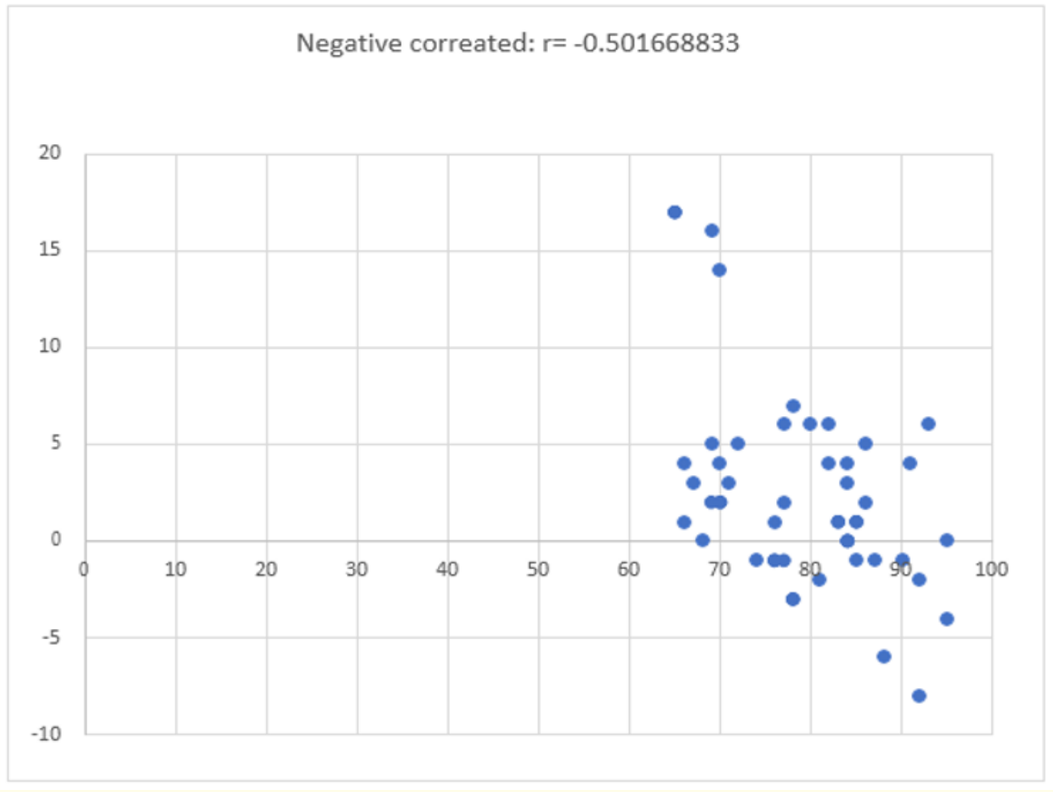

Figure 1: *Age and increased femoral bone mineral density.*

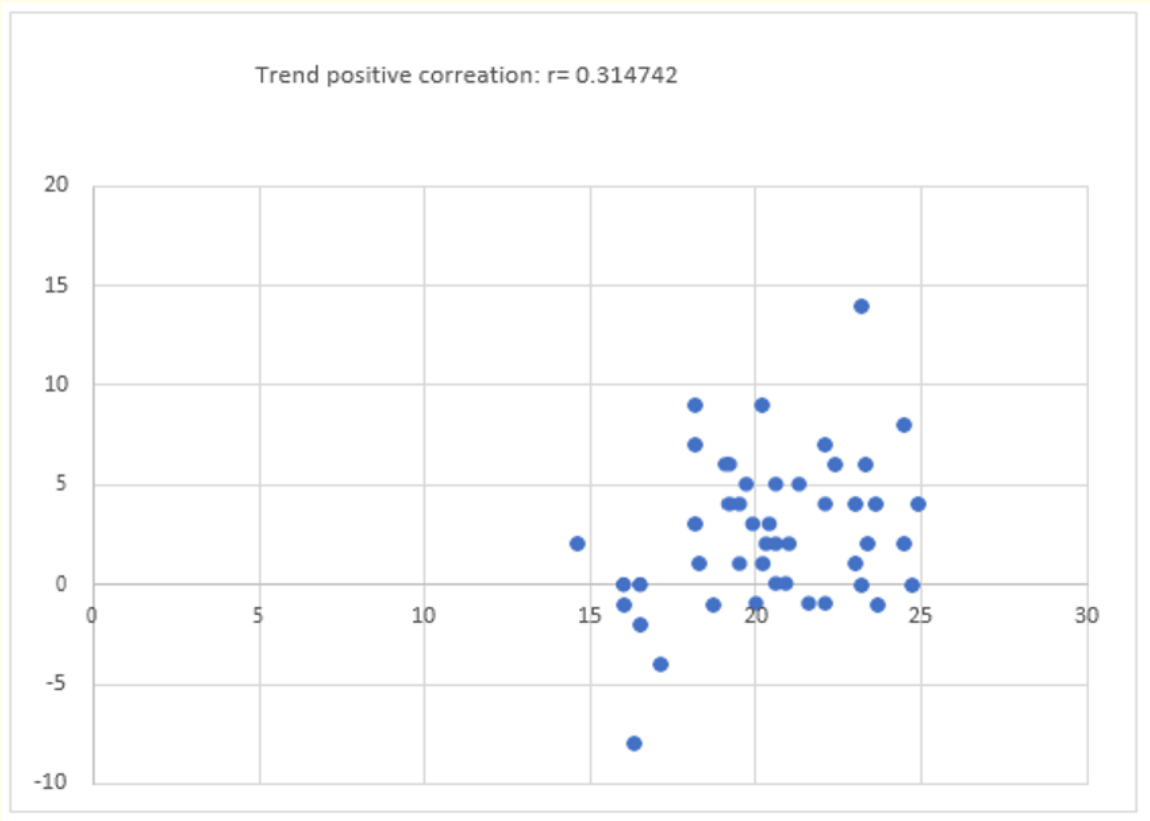

Figure 2: *Body mass index and increased femoral bone mineral density.*

Representative cases

Case 1: A 65-year-old woman with postmenopausal osteoporosis with a BMI of 18.2 kg/m^2. She could perform independent gait and did not have complications or a history of surgery. Following treatment with VD (Edirol®) and BP (risedronate), her F-BMD decreased from 67% to 62%. Because a painless vertebral compression fracture occurred, treatment was switched to VD + Zol infusion. After the administration of two courses, her F-BMD increased from 62% to 79%, and the bone resorption marker (cross-linked N-terminal telopeptides [NTx]) level decreased from 18.0 to 13.4. During the study period, we did not observe low-trauma fractures or adverse reactions. The case patient was a relatively young, lean woman without complications or a history of surgery.

Case 2: A 92-year-old woman with osteoporosis with a BMI of 16.3 kg/m^2.

This patient was kyphotic and had undergone a surgery for a bilateral proximal femoral fracture. She was also hypertensive and had chronic gastritis and dementia. She used complete dentures and was chair- and/or bed-bound. Because she had been treated with VD alone, Zol infusion was initiated. Although two courses were administered, her F-BMD decreased from 52% to 44%, and her NTx level increased from 10.1 to 21.6. This was a case of an extremely advanced age patient with a low BMI, complications, a history of surgery and high need of care.

Discussion

The efficacy of Zol infusion has been proven to increase the bone mineral density of the lumbar vertebrae and femur. This study included very advanced aged and lean Japanese women, and despite its small sample size, it demonstrated that Zol infusion was less effective in increasing F-BMD in (1) women with a low BMI, (2) those of a very advanced age, and (3) those with a history of surgery. In the past, Study

H2301: HORAIZON-Pivotal Fracture Trial [4] demonstrated a decreased response in patients with a BMI < 18.5 kg/m^2, whereas no study is present on very advanced age to the best of our knowledge. Regarding surgical history, Study L2310: HORIZON- Recurrent Fracture Trial [5] showed that the effect for preventing clinical fractures was 35%, reporting no difference between patients with and without a history of surgery. However, this past study included patients aged up to 89 years but no advanced age patients of 90 years and older, unlike in the present study. Regarding CKD, the AK156-III-1: ZONE study [6] reported that the incidence of adverse events associated with renal function was 3.9% in the Zol group and 0.6% in the placebo group. Therefore, we considered CKD in the present study. When the analysis was limited to seven women aged 90 years and older, F-BMD increased by a mean of 1.4% (range, -8% to 9%) after treatment. Because Japan now has reached an era when people commonly live up to 100 years, various drugs for very advanced age citizens need to be assessed in future studies.

Conclusion

During the study period, Zol infusion was not discontinued in any patients and the incidence of low-trauma fractures was only 6%. This was deemed to be an effective treatment procedure that can be administered even for lean, very advanced age patients. Zol infusion can be reliably administered rapidly over 15 minutes once a year, and zoledronate is an effective drug for elderly and lean Japanese women as long as CKD is considered.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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