Review Article
Safety of the cathepsin K inhibitor odanacatib in postmenopausal women with osteopenia or osteoporosis: a meta-analysis

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Abstract: Cathepsin K, a cysteine protease expressed in osteoclasts, degrades type 1 collagen. Odanacatib selectively and reversibly inhibited cathepsin K and rapidly decreased bone resorption in preclinical and clinical studies. By searching the PubMed, Embase, OVID and Science Direct databases, we conducted a meta-analysis to examine the safety of odanacatib in postmenopausal women with osteoporosis. Studies were pooled, and the relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated. Version 12.0 STATA software was used for statistical analysis. Six relevant articles were included for this meta-analysis study. We observed that the incidence of fracture in postmenopausal women treatment with odanacatib is significantly lower than that with placebo (RR=0.34, 95% CI=0.16-0.71, \( P_{\text{heterogeneity}} < 0.750, I^2 = 0 \)), however, there was no significant difference in the incidence of AEs, SAEs, discontinuations due to AEs and skin AEs. In conclusion, compared to placebo, odanacatib treatment significantly reduced the risk of relative fracture, however, there was no difference between the safety of odanacatib and placebo. Odanacatib is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future.

Keywords: Odanacatib, osteoporosis, meta-analysis, randomized controlled trials

Introduction
Menopause is associated with decreased estrogen levels and subsequent change in bone density [1]. This relationship is the result of bone remodeling imbalance, which occurs with aging and menopause. Bone loss that follows this imbalance, leading to a change in bone structure and a reduction in bone mineral density (BMD) [2, 3]. Osteoporosis is a significant and increasingly important clinical conditions. An estimated 30% of all postmenopausal women in the United States and Europe have osteoporosis, the prevalence of this situation is expected to increase as the world population ages, lead to increased health care costs [4]. With the ageing of population aging, China was experiencing a growing epidemic of osteoporosis. About one third of the women aged 60-69 years and half of those aged 70 years or over have osteoporosis [5].

Cathepsin K is a key enzyme expressed predominantly in osteoclasts, which involved in the degradation of organic bone matrix. Inhibiting bone resorption found in animal models and human deficient for cathepsin K has identified this enzyme as a suitable target, intervention for small molecules with potential as a therapeutic agent in the treatment of osteoporosis [6]. Odanacatib (ODN) is a non-basic selected cathepsin K inhibitor with good pharmacokinetic parameters such as long half-life, minimal in vitro metabolism, as well as oral bioavailability. In preclinical studies, ovary removal of monkeys and rabbits by ODN showed significantly inhibited bone resorption markers along with increase of bone mineral density (BMD) [7, 8]. The effects of ODN treatment in comparison with those of other antiresorptive agents (e.g. bisphosphonates and denosumab) were significant differences. ODN showed specific effects on trabecular versus cortical bone formation, resulting in significant increases in cortical thickness and periosteal bone formation in ovary removal of monkeys whereas trabecular bone formation was reduced [7, 8].
In recent years, several randomized controlled trials (RCTs) have been conducted to evaluate the safety of ODN in the treatment of postmenopausal osteoporosis in women [9-13]. However, the results were not consistent. Therefore, the safety of ODN for the treatment of postmenopausal osteoporosis in women should be systematically evaluated. Here in this study, we performed a meta-analysis of eligible studies to assess the safety of ODN in postmenopausal women with osteoporosis.

Materials and methods

Search strategy

PubMed, Embase, OVID, Science Direct databases were searched for RCTs using the following terms and their combinations: 1) odanacatib, 2) osteopenia or osteoporosis, and 3) postmenopausal women. And the last research was updated on Nov. 2015. All searched studies were screened and their references were retrieved to obtain other related articles. Then we downloaded the relevant papers and further screened to identify potentially eligible studies.

Selection criteria

The inclusion criteria included: 1) eligibility is limited to randomized controlled trials (RCT) in postmenopausal women with osteoporosis; 2) study compared the safety of odanacatib in treatment of osteoporosis. The exclusion criteria included: 1) clinical cases; 2) literature revi-
Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. The safety outcomes included: (1) Adverse events (AEs); (2) Serious adverse events (SAEs); (3) Skin AEs; (4) Discontinuations due to AEs; (5) Fractures.

Statistical analysis

All results summarized using STATA Software (version 12, StataCorp, College Station, TX). We calculated the risk ratio (RR) and 95% confidence intervals for dichotomous data. Preliminary analysis using a fixed effect model (Mantel-Haenszel method), if there are study heterogeneity ($P<0.1$), using a random effects model. By Begg’s funnel plot and Egger’s test to assess publication bias visually evaluated symmetry ($P<0.05$ was considered statistically significant).

Results

Characteristics of the studies

There were 147 papers relevant to the search words. Subsequently, 106 irrelevant articles were excluded. The remaining articles were systematically reviewed, and 20 articles qualified for full-text reading. After full-text reading, 15 articles were deemed unsuitable and were therefore excluded, and 5 articles were identified to be included for qualitative analysis. Finally, 5 studies composed of 948 osteoporosis patients were incorporated into the current meta-analysis. The flow chart of selection of studies and reasons for exclusion is presented in Figure 1. The main characteristics of the eligible studies were shown in Table 1.

Quantitative synthesis

The five studies were included in the meta-analysis of adverse events.

Adverse events (AEs): This outcome was reported in 4 trials, all comparing odanacatib to placebo. There was no heterogeneity between the study ($P=0.473$, $I^2=0$%), the fixed effect model was used. There was no significant difference in the incidence of adverse events (RR=0.99, 95% CI: 0.92~1.06), as shown in Figure 2A.

Serious adverse events (SAEs): This outcome was reported in four trials, all comparing odanacatib to placebo. There was no heterogeneity between the study ($P=0.503$, $I^2=0$%), the fixed effect model was used. There was no significant difference in the incidence of serious AEs (RR=1.11, 95% CI: 0.77~1.59), as shown in Figure 2B.

Discontinuations due to AEs: This outcome was reported in 4 trials, all comparing odanacatib to placebo. There was no heterogeneity between the study ($P=0.502$, $I^2=0$%), the fixed effect model was used. However, there was significant difference in the incidence of discontinuations due to AEs (RR=1.61, 95% CI: 0.93~2.76), as shown in Figure 2C.

Skin AEs: This outcome was reported in five trials, all comparing odanacatib to placebo. There was no heterogeneity between the study ($P=0.586$, $I^2=0$%), the fixed effect model was used. However, there was significant difference in the incidence of skin AEs (RR=0.86, 95% CI: 0.64~1.16), as shown in Figure 2D.

Fractures: This outcome was reported in two trials, all comparing odanacatib to placebo. There was no heterogeneity between the study ($P=0.750$, $I^2=0$%), the fixed effect model was used. However, there was significant difference in the incidence of fractures (RR=0.34, 95% CI: 0.16~0.71), as shown in Figure 2E.

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Table 1. Characteristics of randomized controlled trials included in this meta-analysis

<table>
<thead>
<tr>
<th>Authors/year of publication</th>
<th>Drug, dose and No randomized</th>
<th>Duration (months)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/2010 [9]</td>
<td>50 mg (n=78)</td>
<td>24</td>
<td>Total AEs, SAEs, Discontinuations due to AEs, Skin AEs</td>
</tr>
<tr>
<td>Eisman/2011 [10]</td>
<td>50 mg (n=97)</td>
<td>36</td>
<td>Total AEs, SAEs, Discontinuations due to AEs, Skin AEs</td>
</tr>
<tr>
<td>Langdahl/2012 [11]</td>
<td>50 mg (n=100)</td>
<td>60</td>
<td>Total AEs, SAEs, Discontinuations due to AEs, Skin AEs</td>
</tr>
<tr>
<td>Bonnick/2013 [12]</td>
<td>50 mg (n=122)</td>
<td>24</td>
<td>Total AEs, SAEs, Discontinuations due to AEs, Skin AEs, incidence of fracture</td>
</tr>
<tr>
<td>Brixen/2013 [13]</td>
<td>50 mg (n=109)</td>
<td>N=105</td>
<td>Skin AEs, incidence of fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total AEs: Total Adverse events; SAEs: Serious Adverse events; NA: Not available.</td>
</tr>
</tbody>
</table>
Odanacatib in osteopenia or osteoporosis

A Study ID RR (95% CI) Weight
Bone (2010) 1.00 (0.91, 1.09) 26.02
Eisman (2011) 0.97 (0.84, 1.13) 26.49
Langdahl (2012) 1.11 (0.94, 1.31) 16.32
Bonnick (2013) 0.92 (0.79, 1.09) 31.17
Overall (I-squared = 0.6%, p = 0.473) 0.99 (0.92, 1.06) 100.00

B Study ID RR (95% CI) Weight
Bone (2010) 1.86 (0.83, 4.19) 16.36
Eisman (2011) 1.19 (0.49, 2.87) 17.33
Langdahl (2012) 0.92 (0.44, 1.95) 23.94
Bonnick (2013) 0.89 (0.50, 1.60) 42.37
Overall (I-squared = 0.6%, p = 0.503) 1.11 (0.77, 1.59) 100.00

C Study ID RR (95% CI) Weight
Bone (2010) 1.26 (0.60, 2.64) 54.69
Eisman (2011) 0.95 (0.24, 3.68) 21.07
Langdahl (2012) 2.91 (0.15, 55.13) 3.62
Bonnick (2013) 2.98 (0.99, 8.97) 20.61
Overall (I-squared = 0.6%, p = 0.502) 1.61 (0.93, 2.76) 100.00

Odanacatib in osteopenia or osteoporosis


In a particularly high risk of osteoporosis after menopause, women lack of estrogen usually has a high rate of bone remodeling and bone absorption than bone formation. The result is bone loss, bone fragility and increased risk of fractures. Good method can be used in the measurement of bone mineral density in clinical practice now, the assessment of fracture risk, and treatment of patients with drug preparation, appropriate to reduce their risk of fractures.

Odanacatib is a specific inhibition of cathepsin K, is secreted by the cells broken bone.

Publication bias

Finally, the Egger’s regression test showed no evidence of asymmetrical distribution in the funnel plot in incidence of adverse events (Begg’s test P=1.000; Egger’s test P=0.924) and incidence of skin AEs (Begg’s test P=1.000; Egger’s test P=0.895) (Figure 3).

Discussion

WHO determines the osteoporosis as a major public health problem, due to its high prevalence and the consequences of osteoporotic fracture. In a particularly high risk of osteoporosis after menopause, women lack of estrogen usually has a high rate of bone remodeling and bone absorption than bone formation. The result is bone loss, bone fragility and increased risk of fractures. Good method can be used in the measurement of bone mineral density in clinical practice now, the assessment of fracture risk, and treatment of patients with drug preparation, appropriate to reduce their risk of fractures.
Odanacatib in osteopenia or osteoporosis

Odanacatib is a cathepsin K inhibitor extensively studied in clinical trials and is the sole remaining agent in clinical development. In preclinical studies, the use of CATK inhibitors in ovariectomized rabbits and monkeys induced dose-dependent reduction of bone resorption in trabecular and cortical sites and preservation of areal BMD [20-24]. Odanacatib treatment increased the number of osteoclast when assessed by histomorphometry, and elevated serum levels of tartrate resistant acid phosphatase 5b (TRAP5b). The effects of CatK inhibition on bone formation are more complex. Like other resorption inhibitors, balicatib and odanacatib inhibit trabecular bone formation in ovariectomized monkeys. In the 2 phase of the placebo controlled clinical trial, postmenopausal women with low BMD received odanacatib at a dose ranging from 3 to 50 mg per week [9]. More than 24 months of treatment, observed a dose-dependent increase in the lumbar spine and femoral neck bone mineral density. At the highest dose (50 mg odanacatib weekly), BMD increased 5.7% and 4.1% at the lumbar spine and hip, respectively, versus placebo. The effects of treatment with odanacatib on the incidence of fracture is being assessed in an international, phase 3 placebo-controlled study in more than 16,000 postmenopausal women with osteoporosis [19]. According to the results of a pre-planned interim analysis, this study was recently stop early because of “powerful effectiveness”. After a average duration of therapy of approximately 3 years, it was recently reported that odanacatib significantly reduced the incidence of vertebral, non-vertebral and hip fractures [25].

Several limitations in this meta-analysis should be addressed. First, our study may be impaired, to extract the raw data from including research. Secondly, the language can also introduce a bias. Specifically, we select only the English lan-

![Funnel plot with pseudo 95% confidence limits](image)

**Figure 3.** Begg’s funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Incidence of adverse events; B. Incidence of skin AE.

Bone type I collagen degradation enzymes. Increase bone mineral density in the spine and hip after effects, withdrawal immediately reversible [11]. Preliminary data, in the United States Society for Bone and Mineral Research (ASBMR) 2014, showed a significant reduction in the risk of vertebral, non-vertebral and hip fractures [19]. The results of this meta-analysis including 5 RCTs indicate that treatment of postmenopausal women with odanacatib is associated with reduced risk of relative fracture as compared with those that received placebo and adverse event rates during treatment period were similar between groups. These results indicate that odanacatib can cause a significant reduction in relative fracture risk in the odanacatib compared with the placebo group.
Odanacatib in osteopenia or osteoporosis
guage and exclude other qualified researchers. A third of a potential limitation is that the assessment data sets were considered too little for visual or statistical examination of publication bias, and the potential presence of such bias could not be determined. Therefore, we hypothesized that publication bias might be present.

In conclusion, compared to placebo, odanacatib treatment significantly reduced the risk of relative fracture, however, there was no difference between the safety of odanacatib and placebo. Odanacatib is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future. However, due to the existence of the unstable factors, furthermore studies need to be done to verify the result of this study.

Disclosure of conflict of interest

None.

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References


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