Effect of denosumab, a fully human monoclonal antibody to RANKL, on bone mineral density and fractures: a meta-analysis

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Abstract: Receptor activator of nuclear factor κB ligand (RANKL) is the principal regulator of osteoclast differentiation, activity, and survival; denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and is approved for the treatment of women with postmenopausal osteoporosis at high risk of fractures. By searching the PubMed and Embase databases, we conducted a meta-analysis to examine the bone mineral density (BMD) and the fracture rate in osteoporosis patients being treated with denosumab. Studies were pooled, and mean difference (MD), the relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated. Twelve relevant articles were included for this meta-analysis study. Compared to placebo, denosumab treatment significantly decreased the risk of fracture (RR = 0.42, 95% CI = 0.27-0.68, \( P_{\text{heterogeneity}} = 0.005, I^2 = 73.1\% \)) and increased the percent change in bone mineral density at the total hip (MD = 5.06%, 95% CI = 4.76-5.36, \( P_{\text{heterogeneity}} < 0.001, I^2 = 99.7\% \)) and lumbar spine (MD = 7.6%, 95% CI = 6.91-8.30, \( P_{\text{heterogeneity}} < 0.001, I^2 = 99.9\% \)). Compared to alendronate, denosumab treatment significantly increased the percent change in bone mineral density at the total hip (MD = 1.18%, 95% CI = 1.00-1.35, \( P_{\text{heterogeneity}} < 0.001, I^2 = 98.1\% \)) and lumbar spine (MD = 1.36%, 95% CI = 0.96-1.76, \( P_{\text{heterogeneity}} < 0.001, I^2 = 99.3\% \)), however, there was no significant difference in the incidence of fractures. In conclusion, these results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in fractures risk in the denosumab compared with the placebo group.

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

Introduction

Osteoporosis is a common bone disease, which is characterized by low bone density (BMD) and poor bone quality, reduced bone strength and increased risk of fractures [1]. It is a global public health problem, affecting more than 75 million people in the United States, Europe and Japan, leading to more than 8.9 million fractures each year around the world [2]. In the United States, approximately 44 million people suffering from osteoporosis or low bone mass (osteopenia) increased risk of fracture [3]. With the aging of the population growing, China is experiencing an increasing the prevalence of osteoporosis. About a third of women aged 60-69 years and a half of over the age of 70 years have osteoporosis [4].

In the past few decades, osteoporosis treatment greatly expanded. Introducing a nitrogen-containing bisphosphonates, by inhibiting bone resorption, it has been an important step forward [5-8]. Parathyroid hormone (PTH) and teriparatide also help prevent fractures, but in general it is critically ill patients due to a variety of factors, including cost and inconvenience of daily injections [9]. Denosumab treatment program approved by the further expansion [10]. Denosumab, a human monoclonal antibodies, specific binding and receptor-activating factor nuclear factor Kappa B ligand (RANKL) and...
Denosumab on bone mineral density and fractures

Thus reduce bone resorption, has launched for the treatment of postmenopausal osteoporosis. Use of either zoledronic acid administered once yearly as an iv infusion [11] or denosumab administered sc every 6 months [10] decreased bone turnover, increase bone mineral density (BMD), and reduce the risk of vertebral and non-vertebral and hip fractures.

In recent years, several randomized controlled trials (RCTs) have been conducted to evaluate the BMD and the fracture rate in osteoporosis patients being treated with denosumab [10, 12-22]. However, the results were not consistent. Therefore, the BMD and the fracture rate of denosumab therapy in patients with osteoporosis should be systematically evaluated. Here in this study, we performed a meta-analysis of eligible studies to assess the BMD and the fracture rate of denosumab therapy in patients with osteoporosis.

Materials and methods

Search strategy

A comprehensive literature searching of Pubmed and Embase database was conducted. The search strategy included the combinations of the following key words: Denosumab AND osteoporosis AND (bone mineral density OR fracture). The last search was updated on January 20th, 2016. We also manually checked the reference list to identify additional publications. The published language was limited to English.

Selection criteria

The inclusion criteria included: 1) eligibility is limited to randomized controlled trials (RCT) in patients with osteoporosis; 2) study evaluated the BMD and the fracture rate in osteoporosis patients being treated with denosumab. We excluded clinical cases, literature reviews, commentaries, letters to the editor, and experimental studies.

Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. The outcomes were: (1) BMD T-scores of lumbar spine; (2) BMD T-scores of total hip; (3) Fractures. If the data were not reported in the original article, we extrapolated them from the accompanying graphs.

Statistical analysis

We calculated the mean difference (MD) and 95% confidence intervals (CI) for the continuous data, and calculate the risk ratio (RR) and 95% confidence intervals for dichotomous data. Data was combined according to random effects (DerSimonian and Laird’s method) or fixed effects model, depending on the significance of the $I^2$ statistic. If the heterogeneity was significant, random effects model was used; otherwise the fixed effects model was used. Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall’s tau and Egger bias test ($P < 0.05$ was considered statistically significant). All results were summarized using STATA Software (version 12, StataCorp, College Station, TX).
Denosumab on bone mineral density and fractures

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Drug, dose and No randomised</th>
<th>Duration (months)</th>
<th>Evaluation criteria</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClung [12]</td>
<td>2006</td>
<td>Denosumab 60 mg (n = 46)</td>
<td>Placebo (N = 46)</td>
<td>12</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
<tr>
<td>Lewiecki [13]</td>
<td>2007</td>
<td>30 mg (n = 41)</td>
<td>Alendronate 70 mg (N = 47)</td>
<td>24</td>
<td>BMD-T-scores Lumbar spine and total hip</td>
</tr>
<tr>
<td>Bone [14]</td>
<td>2008</td>
<td>60 mg (n = 166)</td>
<td>Placebo (N = 166)</td>
<td>24</td>
<td>BMD-T-scores Lumbar spine and total hip</td>
</tr>
<tr>
<td>Cummings [10]</td>
<td>2009</td>
<td>60 mg (n = 3902)</td>
<td>Placebo (N = 3906)</td>
<td>36</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
<tr>
<td>Smith [15]</td>
<td>2009</td>
<td>60 mg (n = 734)</td>
<td>Placebo (N = 734)</td>
<td>36</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
<tr>
<td>Brown [16]</td>
<td>2009</td>
<td>60 mg (n = 594)</td>
<td>Alendronate 70 mg (N = 595)</td>
<td>12</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
<tr>
<td>Kendler [17]</td>
<td>2010</td>
<td>60 mg (n = 253)</td>
<td>Alendronate 70 mg (N = 251)</td>
<td>12</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
<tr>
<td>Bone [18]</td>
<td>2011</td>
<td>60 mg (n = 128)</td>
<td>Placebo (N = 128)</td>
<td>48</td>
<td>BMD-T-scores Lumbar spine and total hip</td>
</tr>
<tr>
<td>Jamal [19]</td>
<td>2011</td>
<td>60 mg (n = 423)</td>
<td>Placebo (N = 410)</td>
<td>36</td>
<td>NA Incidence of fracture</td>
</tr>
<tr>
<td>Nakamura [20]</td>
<td>2012</td>
<td>60 mg (n = 54)</td>
<td>Placebo (N = 55)</td>
<td>12</td>
<td>BMD-T-scores Lumbar spine and total hip</td>
</tr>
<tr>
<td>Freemantle [21]</td>
<td>2012</td>
<td>60 mg (n = 106)</td>
<td>Alendronate 70 mg (N = 115)</td>
<td>12</td>
<td>NA Incidence of fracture</td>
</tr>
<tr>
<td>Nakamura [22]</td>
<td>2014</td>
<td>60 mg (n = 472)</td>
<td>Placebo (N = 480) Alendronate 35 mg (N = 242)</td>
<td>24</td>
<td>BMD-T-scores Lumbar spine, total hip and incidence of fracture</td>
</tr>
</tbody>
</table>

BMD: Bone mineral density; NA: Not available.
Denosumab on bone mineral density and fractures

Results

Characteristics of the studies

The PRISMA flow diagram of studies is depicted in Figure 1. The last electronic search was conducted in January 20, 2016 and identified 626 relevant literatures in the Pubmed search and 717 sources through Embase. After removing repeat references and related articles, there are 36 records is restricted to full-text reading. Nineteen publications meet the inclusion criteria, while others have no choice for various reasons (e.g., studies not reporting on BMD/fragments or without a control group). A total of 12 studies were included in the qualitative synthesis, and the data from these studies were included in the meta-analysis.

Table 1 Provides a summary of the studies included in the meta-analysis. There were 14,140 participants were included in this meta-
Denosumab on bone mineral density and fractures

Sample sizes ranged from 92 to 7808. These studies were published in 2006-2014.

**Quantitative synthesis**

The seven studies provided numerical data regarding the percent change in BMD of the lumbar spine from baseline between patients who received denosumab and placebo, and were included in the meta-analysis. There was evidence of heterogeneity among the 7 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 7.6%, 95% CI = 6.91-8.30, $P_{\text{heterogeneity}} < 0.001, I^2 = 99.9\%$) had significantly increased BMD of the lumbar spine compared with patients who received placebo (Figure 2A).

The 7 studies also provided total hip BMD data, and were included in the analysis. There was evidence of heterogeneity among the 7 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 5.06%, 95% CI = 4.76-5.36, $P_{\text{heterogeneity}} < 0.001, I^2 = 99.7\%$) had significantly increased

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**Figure 3.** Efficacy outcomes of percentage change in BMD in randomised controlled trials of denosumab versus alendronate. A. Lumbar spine; B. Total hip.

### Table A: Effect of denosumab on percentage change in BMD of the lumbar spine

<table>
<thead>
<tr>
<th>Study ID</th>
<th>MD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCLung (2006)</td>
<td>0.11 (0.00, 0.12)</td>
<td>19.40</td>
</tr>
<tr>
<td>Lovenkild (2007)</td>
<td>2.76 (2.36, 3.16)</td>
<td>19.47</td>
</tr>
<tr>
<td>Brown (2009)</td>
<td>1.00 (0.87, 1.13)</td>
<td>20.61</td>
</tr>
<tr>
<td>Lonblad (2010)</td>
<td>1.17 (0.84, 1.50)</td>
<td>20.32</td>
</tr>
<tr>
<td>Salamanca (2014)</td>
<td>1.47 (1.01, 1.69)</td>
<td>20.31</td>
</tr>
<tr>
<td>Overall (I^2 = 79.9%, p = 0.000)</td>
<td>1.39 (1.16, 1.60)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis

### Table B: Effect of denosumab on percentage change in BMD of the total hip

<table>
<thead>
<tr>
<th>Study ID</th>
<th>MD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCLung (2006)</td>
<td>1.41 (1.30, 1.52)</td>
<td>19.72</td>
</tr>
<tr>
<td>Lovenkild (2007)</td>
<td>1.71 (1.50, 1.92)</td>
<td>18.10</td>
</tr>
<tr>
<td>Brown (2009)</td>
<td>0.49 (0.30, 0.68)</td>
<td>21.34</td>
</tr>
<tr>
<td>Lonblad (2010)</td>
<td>0.85 (0.80, 0.90)</td>
<td>20.04</td>
</tr>
<tr>
<td>Salamanca (2014)</td>
<td>1.36 (1.01, 1.71)</td>
<td>20.40</td>
</tr>
<tr>
<td>Overall (I^2 = 79.1%, p = 0.000)</td>
<td>1.36 (1.03, 1.75)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis
BMD of the total hip compared with patients who received placebo (Figure 2B).

The five studies provided numerical data regarding the percent change in BMD of the lumbar spine from baseline between patients who received denosumab and alendronate, and were included in the meta-analysis. There was evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 1.36%, 95% CI = 0.96-1.76, \(P_{\text{heterogeneity}} < 0.001, I^2 = 99.3\%\) had significantly increased BMD of the lumbar spine compared with patients who received alendronate (Figure 3A).

The 5 studies also provided total hip BMD data, and were included in the analysis. There was evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 1.18%, 95% CI = 1.00-1.35, \(P_{\text{heterogeneity}} < 0.001, I^2 = 98.1\%\) had significantly increased BMD of the total hip compared with patients who received alendronate (Figure 3B).
The five studies provided fracture data between patients who received denosumab and placebo, and were included in the meta-analysis. There was no evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference indicated that patients who received denosumab (RR = 0.42, 95% CI = 0.27-0.68, \( P_{\text{heterogeneity}} = 0.005, I^2 = 73.1\% \)) had significant difference in the incidence of fractures compared with patients who received alendronate (Figure 4A).

**Discussion**

Fractures are due to many factors, including factors increase the risk of bone fragility and risk of falling [23]. Bone fragility, the final approach is the degree and quality of bone metabolism and bone remodeling balance [24]. In most of the risk of bone fractures in women after menopause, bone remodeling, is expressed as the frequency of activation of the bone remodeling unit, and increased [25]. Therefore, bone resorption treatment resistance, reduce the rate of bone turnover has grown as the main way to prevent fractures.

Currently, the most commonly used antiresorptive drugs are bisphosphonates (BPs) and denosumab. Nitrogen-containing BPs bind to bone surface and inhibit the mevalonate pathway, leading to apoptosis of osteoclasts, inhibiting ceased effective BPs can last for a very long time, such as alendronate and zoleodronic..
Denosumab on bone mineral density and fractures

Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor κB ligand (RANKL) and so inhibit the differentiation and activation of osteoclasts in six months, a suppression resolve one year after stopping [27]. The aim of this meta-analysis was to evaluate the bone mineral density (BMD) and the fracture rate in osteoporosis patients comparing denosumab to placebo or alendronate. Compared to placebo, denosumab treatment significantly decreased the risk of fracture and increased the percent change in bone mineral density at the total hip and lumbar spine. Compared to alendronate, denosumab treatment significantly increased the percent change in bone mineral density at the total hip and lumbar spine, however, there was no significant difference in the incidence of fractures. These results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in relative fracture risk in the denosumab compared with the placebo group.

Denosumab is the first specific biotherapy authorized and reimbursed for the treatment of postmenopausal osteoporosis. In the FREEDOM study, patients with vertebral and non-vertebral fractures were significantly lower in the denosumab treatment group. At 12, 24 and 36 months the risk reduction was 61%, 71% and 68% for vertebral fractures and 20%, 21% and 16% for non-vertebral fractures, respectively. In three years, reduce the risk of hip fracture by 40% [10, 28]. Wrist fractures decreased risk and severity of osteoporosis [29]. The most important contribution of denosumab, it can be used for moderate or severe renal dysfunction in patients, because previously not reasonable treatment options [19]. The second advantage of denosumab is the effectiveness of subcutaneous administration. This means that responsibility for adherence passes from the patient alone to the physician and patient together. The persistence of oral treatment for osteoporosis was poor, with all patients stopping at the first year and a half [30].

Several limitations in this meta-analysis should be addressed. First, although we do have a data extraction and repeated high reviewers agreement between the measured data, some information about deviations or measurement errors may occur, because in some trials dispersion measures extracted from the original publications in graphs. Secondly, evaluation of the data set was considered to be too small for visual or statistical examination of publication bias, and the potential existence of such bias could not be determined. Therefore, we assumed that publication bias was probably present. Third, even though we have clear inclusion and exclusion criteria, significant differences in research design, intervention and outcome measurements may have a certain impact on the results.

In conclusion, these results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in relative fracture risk in the denosumab compared with the placebo group. Denosumab is a valuable new option for the treatment of osteoporosis and may be used as a first-line treatment in future. However, further studies are needed to verify the results of the present study due to the presence of an unstable factor.

Disclosure of conflict of interest
None.

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Denosumab on bone mineral density and fractures


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Denosumab on bone mineral density and fractures

5940


