SYSTEMATIC REVIEW

Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis

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SUMMARY
The aim of this study was to perform a head-to-head comparison of efficacy and safety profile between 60 mg denosumab (Den) subcutaneously (SC) per 6 months (Q6M) and 70 mg alendronate (Aln) orally per week (QW) for postmenopausal women with low bone mineral density. We searched electronic databases comparing efficacy and safety of Den SC Q6M and Aln QW in postmenopausal women. The primary outcomes of efficacy evaluation in included trials were incidence of clinical fracture in both groups and bone mineral density (BMD) at different skeletal sites. And adverse events (AEs), including incidence of neoplasms and infections, were considered as secondary outcomes. Following the instructions of ‘Cochrane Handbook for systematic Reviews of Interventions 5.0.2’, we identified eligible studies, evaluated the methodological quality and abstracted relevant data. Four heterogeneous randomised controlled trials (RCTs) involving 1942 women were identified. The results of review showed low evidence quality that supported the hypothesis the denosumab vs. alendronate could reduce risk of fracture [OR (95% CI) 1.42 (0.84 to 2.40), 11 more women per 1000 (from 4 fewer to 36 more), p = 0.19] but the moderate to high quality evidence suggesting treatment with 60 mg Den SC Q6M was more effective for postmenopausal women in increasing BMD [at distal radius (DR), total hip (TH), lumbar spine (LS), and femoral neck (FN)]. Hazards of neoplasms [OR (95% CI) 1.10 (0.65 to 1.86), 3 more per 1000 (from 10 fewer to 24 more), p = 0.62] or infections [OR (95% CI) 0.95 (0.79 to 1.15), 12 fewer per 1000 (from 53 fewer to 33 more), p = 0.62] appeared to be similar. Our review suggested within 1 year 60 mg Den SC Q6M treatment was more effective in increasing bone mass but could not reduce the fracture risk to a greater extent than 70 mg Aln QW therapy. Also, the Den SC Q6M therapy did not increase the risks of neoplasms and infections compared with Aln QW.

Review Criteria
Alendronate is the most widely prescribed class of therapy for osteoporosis; denosumab is a novel agent for osteoporosis with a distinct mechanism from alendronate. Both 60 mg denosumab subcutaneously every 6 month (Den SC Q6M) and 70 mg alendronate orally every week (Aln QW) were reported previously to effectively reduce fracture risk for postmenopausal women with low bone mineral density.

Message for the Clinic
Within 1 year 60 mg Den SC Q6M treatment was more effective in increasing bone mass but could not reduce the fracture risk to a greater extent than 70 mg Aln QW therapy. Also, the Den SC Q6M therapy did not increase the risks of neoplasms and infections compared with Aln QW.

Introduction
Osteoporosis, most cases of which occur in postmenopausal women and is defined by low BMD, is a common contributor to an estimated 90% of all hip and spine fractures in white American women aged 65–84 years (1). The therapeutic goal is to increase the bone mass, improve the bone strength and ultimately to reduce the fracture incidence.

Alendronate (Aln), a classic antiresorptive agent, is one of the most widely prescribed class of therapy for osteoporosis (2). It could significantly reduce the bone turnover by binding to bone and inhibiting the bone resorption (3). Aln was reported to reduce 45% risk of hip fractures of postmenopausal osteoporotic women (4). However, only a few patients fully adhere to its long therapeutic duration because of the gastrointestinal disorder and inconveniences. A recent study reported only 30.6% of patients adhered to one dose of Aln per week (QW) after 1-year treatment (5).

Receptor activator of nuclear factor-κB ligand (RANKL) is a cytokine essential for osteoclast differentiation, activation, and survival (6,7). The RANKL inhibitor denosumab is a fully human monoclonal IgG2 antibody, which potently reduces bone resorption with accompanying increases in bone mineral density (BMD) by binding RANKL. 60 mg Den
subcutaneously (SC) per 6 months (Q6M) as been well documented to improve the patients’ compliance (8), reduce the bone remodeling, and increase the bone mass (9). A significant 42% reduction in fracture incidence could be identified in a recent meta-analysis in postmenopausal women of denosumab treatment compared with the placebo control (10). However, RANK activation by RANKL is also necessary for T-cell growth and dendritic cell function (11,12), inhibition of its action was supposed to simultaneously influence the immune system, leading to high susceptibility of infections and neoplasms (13).

The efficacy of two agents appeared similar according to two recent meta-analysis: when compared with placebo groups, 42% with Den therapy (10) and 45% with Aln treatment (4) in fracture risk reduction could be found respectively. But to our knowledge, the number and sample size of the relevant RCTs performing such head-to-head comparison between both agents was relative small. Until now no meta-analysis had been published on this topic.

Thus, it is meaningful to carry out this meta-analysis to evaluate whether Den would be more effective in reducing risk of fracture and increasing bone mass without increasing the risk of neoplasms and infections in postmenopausal women compared with Aln.

**Materials and methods**

**Literature search**

Electronic databases (Medline, EMBASE and the Cochrane Data Base of Systematic Reviews, the Cochrane Central Register of Controlled Trials) were searched without limit by two independent investigators (Lin and Wang), which were last updated on July 19, 2011. The search used terms and Boolean operators as follows: ‘(denosumab or AMG-162 or RANK) and alendronate’ with highly sensitive searching filter.

**Identification of eligible studies**

The trials were reviewed in which (i) the target population was consisted of treated or untreated postmenopausal women with low bone mass, (ii) the interventions at least included 60 mg Den SC Q6M and 70 mg orally Aln QW, (iii) the outcomes were fracture incidence, BMD changes at different sites and safety profile, and (iv) the trial was RCT. The trials were excluded if (i) patients had a prior history of metastatic bone disease, (ii) phase-I or observational studies, case reports and reviews, (iii) the same RCT was re-analysed and (iv) only abstract was available. Disagreements were resolved through discussion.

**Assessment of study quality**

Two reviewers (Lin and Zhao) independently assessed the study the validity with Cochrane Collaboration’s tool for assessing the risk of bias, which addresses six specific domains such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting (14). Disagreement was evaluated by means of kappa test, and resolved by discussion.

**Data abstraction, conversion and analysis**

For each eligible trial, two of us (Lin and Wang) independently extracted the relevant data and checked the accuracy. Specifically, we abstracted study design, sample size, demographic data (age and years since menopausal), baseline BMD, intervention protocol, duration of the trial, loss to follow-up, trial outcomes (fracture incidence, BMD changes and risks of infections, neoplasms). We asked the first or the corresponding author of each eligible trial to verify the accuracy of the data abstraction as well as our methodological assessment. We used intention-to-treat data from the trials whenever possible. If not available, we used data from the analysis of the available data or the data from the analysis of treatment received. If the data were not reported in the original article, we extrapolated them from the accompanying graphs. In McClung’s study, (15) the incidence of fractures and serious adverse events (SAEs) for Den group was not extractable (attempts to contact the authors were unsuccessful), and thus data from the mixed group receiving different dosages of denosumab were used as surrogates of the meta-analysis. We performed the sensitivity analysis by omitting the trials with surrogate data to assess whether the overall effect could be influenced.

The overall incidences of clinical and radiological fractures in the two groups were our primary outcome. We also evaluated the BMD percentage changes from the baseline at distal radius (DR), total hip (TH), lumbar spine (LS) and femoral neck (FN). BMD was measured by dual-energy X-ray absorptiometry (DXA).

The safety profile comprised the reported incidence of total adverse events (AEs), serious adverse events (SAEs), infections, and neoplasms. We considered the events requiring hospitalisation as SAEs, and total AEs were identified by the findings of the included studies. The fracture incidence and the safety profile outcomes were presented as odds ratio (OR) with 95% confidence intervals (CI) and combined using the Mantel-Haenszel method. BMD data were pooled with the inverse variance method and presented as weighted mean differences (WMD) and 95% CI. We calculated the statistical heterogeneity using a $\chi^2$ test
on N-1 degree of freedom, with the significance at 0.1. We also assessed the inconsistency I^2 using the formula \((Q-df)/Q \times 100\%\), where Q is the \(\chi^2\) statistic and df is its degree of freedom, to describe the percentage of the variability in effect estimates because of the heterogeneity (14). We considered a value greater than 50% as the substantial heterogeneity. Fixed effects model would be applied if there were no statistical heterogeneity among the studies; otherwise, we used the random effects model. The sensitivity analysis was performed through omitting the trials to assess the variation in overall effect. To make better understanding of the comparison of risks of fracture and AEs, the absolute risk reduction/increment was calculated and showed as fewer/more number of women per 1000 possible events.

We could not carry out the funnel plot analysis, the subgroup analysis and the meta-regression due to insufficient trials included in our review. Meta-analysis was conducted using Review Manager 5.1 software. The criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) were used to evaluate the quality of evidence by outcome (16).

Results

Study identification

Literature search initially yielded 86 relevant trials, of which 46 publications were excluded as they did not fulfill the selection criteria based on their titles. From the remaining 40 publications, 33 were excluded on the basis of the abstract. In total, 68 studies were excluded. Of the left seven trials, (15,17–22) four reported data on the same cohort of women yet at different time frames (15). As the long-term data were rare and most of which were derived from the previous studies for the same object, only the trials with 1-year follow up were included. Overall, four studies were included in our meta-analysis (15,17–19) (Figure 1).

Study characteristics

The characteristics of the included four trials (15,17–19) were shown in Table 1. All the trials were double-blinded and placebo-used, international multicenter RCTs, of which two were phase II (15,19) and one was phase III (17). Only postmenopausal women (mean age ranged 60.3–68.2 years) with low bone mass (T-score ranged −1.4 to −2.6) were included in all the studies, which had 1-year follow-up. One study (18) targeted the women with prior alendronate therapy. Considering the treatment history was consistent between both groups, it was not excluded. Morphologic changes were assessed using high-resolution peripheral quantitative computed tomography (HR-pQCT) in one study (19). Two studies directly compared 60 mg Den SC Q6M with 70 mg oral Aln QW (17,18). The other two studies contained a placebo control group as well, one of which adopted the varying dosage of denosumab compared with alendronate and placebo (15). The weighted kappa for the agreement on eligibility between reviewers was 0.87 (95% CI: 0.77–0.96).

Study quality

The methodological quality was evaluated independently by two reviewers (Lin and Zhao) with Cochrane Collaboration’s tool for assessing the risk of bias (14). The randomisation schedules were based on the randomly permuted blocks in all the studies and most of them did not explicitly state their allocation concealment. Three studies claim to apply the intent-to-treat (ITT) analysis (15,17,19) and no
| Author/year/ | Design | Sample size (Den/Aln) | Den group age (Mean ± SD) | Aln group age (Mean ± SD) | Intervention | Duration (months) | Co-factors | Outcome measurement | Loss to follow-up (Den/Aln) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Brown/2009/Canada (17) | Multicenter, international, randomised, double-blind, double-dummy, active-controlled, parallel group, noninferiority phase III study | 594/595 | 64.1(8.6) | 64.6(8.3) | Denosumab | 12 | 500 mg ca 400 or 800 UI vit D | 1. Change in BMD in TH, LS, FA measured by DXA at 1 week, 6 mo and 12 mo 2. Change in CTX and PINP at 1 week, 1, 3, 6, 7, 9, 12 mo 3. AEs and serum chemistry and haematology values | 6%/7% |
| Kendler/2010/Canada (18)* | Multicenter, international, randomised, double-blind, double-dummy study | 253/251 | 66.9(7.8) | 68.2(7.7) | Denosumab | 12 | 1000 mg ca 400 UI vit D | 1. Change in BMD in TH, LP, FA measured by DXA at 1 week, 6 mo and 12 mo 2. Change in CTX and PINP at 1 week, 1, 3, 6, 7, 9, 12 mo 3. AEs and serum chemistry and haematology values | 4%/5% |
| McClung/2006/USA (15) | Multicenter, randomised, plc-controlled, phase II dose-ranging study (eight double-blind + one open label treatment groups) | 412/47/47 | 63.1(8.1) | 62.8(8.2) | Denosumab 6, 14, 30 mg/3 mo, or 14, 60, 100, 210 mg/6 mo, or open label alendronate 70 mg/week for 12 mo | 12 | 1000 mg ca 400 UI vit D | 1. Change in BMD in TH, LS, FA,T8measured by DXA at 1 week, 1, 3, 6, 12 months 2. Change in SCTX, bone ALP; Albumin-Adjusted Serum Calcium, iPTH at 1 weekk, 1, 3, 6, 7, 9, 12 months 3. AEs and serum chemistry and haematology values | 0/2% |
| Seeman/2010 /Australia (19) | International, randomised, double-blind, double-dummy, active-controlled, parallel-group, phase II study | 247/83/82 | 60.3(5.9) | 60.7(5.2) | Denosumab | 12 | 500 mg ca 400 or 800 UI vit D | 1. Change in cortical and trabecular vBMD of distal radius and tibia measured by HR-pQCT; change in QCT parameters of total vBMD and PMI at the distal radial site at 1 week, 6 mo and 12 mo 2. Change in CTX and PINP at 1 week, 1, 3, 6, 7, 9, 12 mo 3. AEs | 11%/16% |

Den, 60 mg denosumab subcutaneously every 6 month; Aln, 70 mg alendronate orally every week; Dif, difference; TH, total hip; LS, lumbar Spine; mo, months Ca, calcium; Vit D, vitamine D; BMD, bone mineral density; vBMD, volumetric BMD; PMI, polar moment of inertia; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; HR-pQCT, high-resolution peripheral QCT; CTX, serum β-C-terminal telopeptide of type 1 collagen; PINP, serum N-terminal propeptide of type 1 procollagen (PINP); AEs, adverse events. *The women received prior alendronate therapy was included in this study.
outcomes were selectively reported in all the studies. Overall, the four studies reported the adequate details of blinding and the loss to follow-up and were of low risk of bias (Table 2). The weighted kappa for the agreement on the trial quality between reviewers was 0.85 (95% CI: 0.75–0.95).

Efficacy of fracture risk reduction

No significant difference in fracture risk was demonstrated between the 60 mg Den SC Q6M group and 70 mg oral Aln QW group at 1 year interval [3 studies, fixed-effects OR (95% CI): 1.42 (0.84–2.40), 11 more women per 1000 (from 4 fewer to 36 more), p = 0.19, I² = 0%, (Figure 2)]. Heterogeneity across studies was insignificant. The sensitivity analysis showed that the overall effect could not be influenced by omitting any single trial. The review only provided low quality evidence that the Den SC Q6M treatment vs. the Aln QW treatment could result in 11 more women per 1000 (from 4 fewer to 36 more) encountering clinical fracture (Table 4).

Efficacy of BMD variation

BMD was measured by DXA at different skeleton sites in three studies (15,17,18). Both 60 mg Den SC Q6M and 70 mg oral Aln QW increased BMD significantly at DR, TH, LS, and FN after 6 months and 12 months compared with the baseline. Den SC Q6M could obtain greater bone mass increment than Aln QW (Table 3). Heterogeneity across studies was significant (p < 0.01) but the sensitivity analysis showed the overall effect could not be influenced by omitting any single trial. The evidence quality was moderate to high (Table 4).

Analysis of safety profiles

Women assigned to either Den Q6M or Aln QW had a similar safety profile in the current review after the one-year interval: [Total AEs: four studies, OR (95% CI) 0.91 (0.72–1.15), 14 fewer per 1000 (from 52 fewer to 19 more), p = 0.66, I² = 0%, (Figure 3A)]. [SAEs: four studies, OR (95% CI) 0.91 (0.63–1.33), 61 fewer per 1000 (from 23 fewer to 20 more), p = 0.65, I² = 0%, Figure 3B]. [Neoplasms: three studies, OR (95% CI) 1.10 (0.65–1.86), 3 more per 1000 (from 10 fewer to 24 more), p = 0.62, I² = 15%, (Figure 3C)]. [Infections: 4 studies, OR (95% CI) 0.95 (0.79–1.15), 12 fewer per 1000 (from 53 fewer to 33 more), p = 0.62, I² = 27%, (Figure 3D)]. The sensitivity analysis showed the overall effect could not be influenced by omitting any single trial. The review only provided low to very low quality of evidence that Den SC Q6M could neither reduce the risk of AEs, SAEs nor increase the hazards of neoplasms and infections compared with Aln QW (See Table 4).

Table 2 Methodological quality of eligible randomised controlled trials

| Study          | Randomised adequately* | Allocation concealed | Blinding† | Selective reporting | Similar co-factors‡ | (%)/Loss to follow-up (Den/Aln) | ITT analysis |
|----------------|------------------------|----------------------|-----------|---------------------|---------------------|---------------------------------|--------------|
| Brown 2009(17) | Inadequately           | Unclear              | Double blinded | No                  | Yes                  | 11%/16%                         | Yes          |
| Kendler 2010(18)| Inadequately           | Unclear              | Double blinded | No                  | Yes                  | 6%/7%                           | Unclear      |
| McClung 2006(15)| Inadequately           | Unclear              | Double blinded | No                  | Yes                  | 0%/2%                           | Yes          |
| Seeman 2010(19)| Inadequately           | Unclear              | Double blinded | No                  | Yes                  | 4%/5%                           | Yes          |

*All studies’s randomisation schedules were based on randomly permuted blocks, which was considered not adequately according to Cochrane Handbook 5.0.2(2008) *†All studies declared double-blind intervention, adequate method of which was described explicitly in three of them (except for McClung’s); outcome assessor was considered to be blinded in all studies though which was clearly stated only in Kendler’s. ‡Calcium and vitamin D were supplemented equally in two groups in all studies.

Figure 2 Fracture risk (one-year interval) for women assigned to Den SC Q6M compared with Aln QW
Table 3  WMD of Bone mineral density (BMD) changes at different sites

| Studies    | Distal radius | Total | WMD       | 12 months |
|------------|---------------|-------|-----------|-----------|
|            | Den           | Aln   | WMD (IV, Ran, 95% CI) | Den   | Aln   | WMD (IV, Ran, 95% CI) |
|            | Mean  | SD    | Total | Mean  | SD    | Total | Mean  | SD    | Total | Weight |
| McGlun 2006 | 2.2   | 0.24  | 46    | 1.3   | 0.26  | 46    | 0.90  | 0.80, 1.00 | 0.04  | 0.25  | 46    | 49.50% | 0.90  | 0.80, 1.00 |
| Kendler 2010 | 0.81  | 0.19  | 253   | 0.4   | 0.18  | 251   | 0.65  | 0.17, 1.13 | 0.04  | 0.25  | 253   | 50.50% | 0.65  | 0.17, 1.13 |
| Total (95% CI) |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Heterogeneity |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Total hip | Brown 2009 | 2.39  | 0.11  | 593   | 1.79  | 0.11  | 586   | 0.60  | 0.59, 0.61 | 3.5   | 0.1   | 593   | 34.40% | 0.60  | 0.59, 0.61 |
| Kendler 2010 | 1.28  | 0.14  | 253   | 0.87  | 0.14  | 251   | 0.41  | 0.39, 0.43 | 1.9   | 0.14  | 253   | 34.20% | 0.41  | 0.39, 0.43 |
| McClun 2006 | 2.58  | 0.23  | 46    | 1.69  | 0.21  | 46    | 0.89  | 0.80, 0.98 | 3.73  | 0.21  | 46    | 31.40% | 0.89  | 0.80, 0.98 |
| Total (95% CI) |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Heterogeneity |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Lumbar spine | Brown 2009 | 3.76  | 0.17  | 593   | 3.03  | 0.15  | 586   | 0.73  | 0.71, 0.75 | 5.3   | 0.17  | 593   | 38.80% | 0.73  | 0.71, 0.75 |
| Kendler 2010 | 1.88  | 0.17  | 253   | 1.11  | 0.16  | 251   | 0.77  | 0.74, 0.80 | 3.03  | 0.19  | 253   | 38.00% | 0.77  | 0.74, 0.80 |
| McClun 2006 | 3.45  | 0.31  | 46    | 3.11  | 0.31  | 46    | 0.34  | 0.21, 0.47 | 4.53  | 0.26  | 46    | 23.10% | 0.34  | 0.21, 0.47 |
| Total (95% CI) |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Heterogeneity |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Femoral neck | Brown 2009 | 1.7   | 0.34  | 593   | 1.1   | 0.4   | 586   | 0.60  | 0.56, 0.64 | 2.4   | 0.4   | 593   | 47.90% | 0.60  | 0.56, 0.64 |
| Kendler 2010 | 1.08  | 0.19  | 253   | 0.42  | 0.21  | 251   | 0.66  | 0.63, 0.69 | 1.4   | 0.21  | 253   | 52.10% | 0.66  | 0.63, 0.69 |
| Total (95% CI) |       |       |       |       |       |       |       |       |       |       |        |        |       |
| Heterogeneity |       |       |       |       |       |       |       |       |       |       |        |        |       |

Den, denosumab; Aln, alendronate; SD, standard deviation; WMD, weighted mean differences IV, inverse variance method; Ran, random effects model; CI, confidential interval.
Discussion

The primary finding is that within 1 year 60 mg Den SC Q6M treatment was more effective in increasing bone mass but could not reduce the fracture risk to a greater extent than 70 mg Aln QW therapy. Also the Den SC Q6M therapy did not increase the risks of neoplasms and infections compared with Aln QW.

Quality of evidence

The findings of the current review were strengthened by strictly following the instruction of ‘Cochrane Handbook for systematic Reviews of Interventions 5.0.2’ (14). Specifically, we developed the explicit criteria of inclusion and exclusion, assessed the methodological quality of the studies, demonstrated the reproducibility of selection, and performed the quantitative analysis. We further limited the selection bias by conducting all aspects of the selection process in duplicate.

We use the GRADE system to rate the quality of evidence for each outcome (shown in Table 4). The eligible trials in our analysis had some limitations: (i) Loss to follow-up leading to incomplete outcome data in some trials, however the rate was acceptable and we did not downgrade the evidence of each outcome, (ii) the substantial heterogeneity, detected in...
the analysis of continuous data, might be resulted from the variability in sample sizes and the selection criteria of the trials: the Kendler's study (18) targeted women with prior alendronate therapy while other trials recruited treated-naive women, therefore we downgraded the evidence; (iii) in McClung's study (15), the surrogate data from the mixed groups receiving different dosages of denosumab were used for the Den Q6M group in the meta-analysis, which might be confounding, and therefore the evidence of dichotomous outcome data was rated down, (iv) the observational duration was only 1 year, and only four trials were included, both of which might weaken the power to detect the difference between both agents, (v) All the included studies were sponsored by the pharmaceutical company related to denosumab. Although we did not rate down the evidence because of the selective reporting bias, the results should be considered with caution. GRADE evidence profile was shown at Table 4.

**Interpretation**

Differences in the mechanism of action of these drugs at tissue and basic multicellular unit (BMU)
levels may explain the superiority of Den SC Q6M over Aln QW groups in increasing BMD (19).

At the cellular level, denosumab prevented the maturation of immature osteoclasts, and suppressed the synthesis, the activity, and the survival of mature osteoclasts as well (6,7). Similarly, at the tissue level, denosumab could inhibit both the formation of new resorption cavities and the osteolysis in existing resorption cavities (23,24). This assumption was further supported by the finding that when women exchanged alendronate for denosumab, the bone biopsies obtained demonstrated less eroded surfaces compared with women with continual administration of alendronate (25). Denosumab, as a circulating antibody, was believed to rapidly bind RANKL and uniformly reach the whole skeleton including the cortical bone.

By contrast, the antiresorptive effect of alendronate gradually followed several steps: firstly, absorbed into blood and binding to bone, secondly taken up by osteoclasts, and finally disrupting the bone resorption and the osteoclast apoptosis (3). This effect may not be so immediate as existing osteoclasts may persist in resorbing bone (19). The strong affinity of alendronate for hydroxyapatite and bone mineral could also narrow the unified distribution throughout the skeleton, particularly to the sites deep within the bone (26).

However, the most important and relevant outcome for the efficacy evaluation was the incidence of fractures. In three included studies they were recorded as adverse events. With significant quality improvement in effective cortical area (DR) with Den SC Q6M therapy compared with Aln QW treatment (19), it was agreed that the compressive strength and resistance to bending would accordingly increase (20), and prevent the non-vertebral fractures resulting from the structural decay of cortical bone (27,28). However, in two previous meta-analysis, 42% and 45% reduction in fracture risk were found with denosumab therapy (10) and alendronate treatment respectively (4) compared with placebo group. Similarly, our review indicated no statistical difference in fracture risk reduction between two groups. It should be noted that the observational period was only 1 year. It needs a longer follow-up of a larger population to draw a more solid conclusion.

The overall rates of AEs and SAEs were balanced between both groups. The rates of infections and neoplasms were particularly concerned because the RANKL inhibition could also affect the immune function (10,11). The present meta-analysis showed the low-quality evidence that denosumab could increase the incidence of infections and neoplasms compared with alendronate. The results of our meta-analysis are consistent with the findings from preclinical (29) and clinical studies (30) which did not suggest that the RANKL/RANK pathway could substantially influence the adult immune system. The potential risk and the safety of long-term denosumab administration should be under surveillance.

In conclusion, the 60 mg Den SC Q6M therapy might be more effective for increasing the bone mass of postmenopausal women than the 70 mg Aln oral QW therapy. However the analysis of the relevant clinical outcome demonstrated inconclusive benefits of denosumab over alendronate, its safety profile was not fully clarified either. At present because of its relatively high price, denosumab could not completely replace alendronate for postmenopausal women.

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Authors’ contributions
S-GY and TL contributed to the study design; TL conducted the study; TL, CW, XZ and M-MS collected the data; TL, CW, X-ZC and Z-MY analysed the data; TL, S-GY, F-ZY, CG and X-ZC interpreted the data; TL and X-ZC drafted the manuscript; TL, S-GY, XZ, Z-MY and X-ZC revised the manuscript content; all authors approved the final version of manuscript and S-GY takes responsibility for the integrity of the data analysis.

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