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Review Article

Efficacy and safety of denosumab and teriparatide treatment for osteoporosis: a systematic review and meta-analysis

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Abstract: Purpose: It may be promising to combine denosumab with teriparatide for the treatment of osteoporosis. However, the results remain controversial. We conduct a systematic review and meta-analysis to evaluate the efficacy and safety of combination treatment (denosumab and teriparatide) versus teriparatide treatment in patients with osteoporosis. Methods: Medline, SCOPUS, Google Scholar, EMBASE, Springer, and Science Direct are searched electronically. Randomized controlled trials (RCTs) or controlled clinical trials (CCTs) regarding the combination treatment versus teriparatide treatment for osteoporosis are included. Two investigators independently search articles, extracted data, and assess the quality of included studies. The primary outcome is the increase in spine bone mineral density (BMD) and hip BMD. Meta-analysis is performed using the fixed-effect model or random-effect model when appropriate. Results: Four studies are included in this meta-analysis. Overall, compared with teriparatide treatment, combination treatment of denosumab and teriparatide significantly increases hip BMD (mean difference = 3.59%; 95% CI = 2.23% to 4.95%; P<0.00001), femoral neck BMD (mean difference = 3.29%; 95% CI = 2.08% to 4.50%; P<0.00001) and radius BMD (mean difference = 3.35%; 95% CI = 2.59% to 4.11%; P<0.00001), but fails to increase spine BMD (mean difference = 1.65%; 95% CI = -1.27% to 4.56%; P = 0.27). Conclusion: Our meta-analysis suggests that combination treatment of denosumab and teriparatide shows an important ability to increase the BMD in patients with osteoporosis. Combination treatment should be recommended to treat osteoporosis, but with caution due to clinical heterogeneity.

Keywords: Denosumab, teriparatide, combination treatment, osteoporosis, meta-analysis

Introduction

Osteoporotic fractures are ubiquitous worldwide and are regarded as the major cause of death, disability, and health-care expenditure [1-3]. And 75% of these patients are women [4, 5]. Despite the development of treatment options, there is still lack of effective therapies to treat osteoporosis and prevent osteoporotic fractures [6, 7].

Current drugs used to treat postmenopausal osteoporosis are mainly divided into two categories: the antiresorptive drugs (e.g. the nitrogen-containing bisphosphonates and the receptor activator of nuclear factor κB ligand (RANKL) inhibitor) and the anabolic drug teriparatide [8-12]. But they are limited by the short time period of use (18-24 months), and sequential use of several drugs is required for severe osteoporosis [13, 14]. Many studies reported that combination treatment using more than two antiresorptive agents showed very limited additive effects on bone mass. For example, combining parathyroid hormone (PTH) with bisphosphonates was not consistently superior to monotherapy [15, 16]. The combination treatment of PTH and raloxifene showed no additive effects on the increase in bone mineral density (BMD) [17].

However, denosumab in combination with teriparatide was revealed to significantly increase BMD of spine and hip compared to either drug alone [18], possibly because of the ability of denosumab not only to fully inhibit teriparatide-induced bone resorption but also to partially inhibit teriparatide-induced bone formation

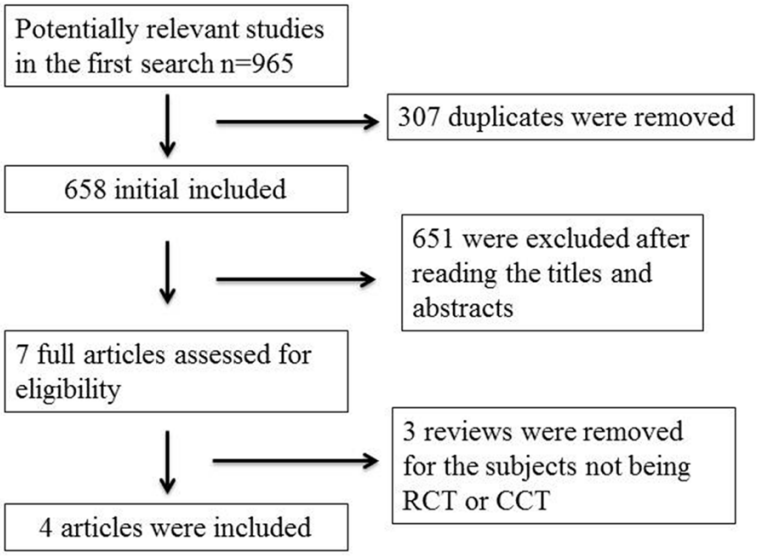

Figure 1. Flow diagram of study searching and selection process.

[19]. In contrast to this promising finding, however, two clinical trials reported that combination treatment of denosumab and teriparatide failed to significantly improve the BMD of spine and femoral neck [20, 21]. Considering these inconsistent effects, we therefore conduct a systematic review and meta-analysis to evaluate the efficacy and safety of combination treatment (denosumab and teriparatide) versus teriparatide treatment for osteoporosis.

Materials and methods

This systematic review and meta-analysis are conducted according to the guidance of the *Preferred Reporting Items for Systematic Reviews and Meta-analysis statement* [22] and the *Cochrane Handbook for Systematic Reviews of Interventions* [23].

Literature search and selection criteria

Medline, SCOPUS, Google Scholar, EMBASE, Springer, and Science Direct are systematically searched from inception to October 2016, with the following keywords: osteoporosis, denosumab and teriparatide. The reference lists of retrieved studies and relevant reviews are also hand-searched.

The inclusion criteria are as follows: study population, patients with osteoporosis; intervention, combination treatment of denosumab and teriparatide; control, teriparatide treatment; outcome, spine BMD, hip BMD, femoral neck BMD, radius BMD; and study design, RCT or CCT.

The exclusion criteria include: hypercalcaemia, hyperparathyroidism, congenital or acquired bone disease, history of malignant disease and radiation therapy.

Data extraction and outcome

The following information is extracted for the included studies: first author, publication year, sample size, baseline characteristics of patients, intervention of combination treatment using denosumab and teriparatide, intervention of control (teriparatide treatment), study design, spine BMD, hip BMD, femoral neck BMD, radius BMD. The authors would be contacted to acquire the data when necessary.

The primary outcome include spine BMD and hip BMD. Secondary outcome are femoral neck BMD and radius BMD.

Quality assessment in individual studies

Two reviewers independently perform data extraction and quality assessment. Four items are used to assess the quality of included studies based on *Cochrane Collaboration recommended criteria*: adequate sequence generation, allocation concealment, blinding, and addressing the problem of incomplete outcome data.

Statistical analysis

Mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcome (spine BMD, hip BMD, femoral neck BMD, and radius BMD) are applied to estimate the pooled effects. Heterogeneity is tested using the Cochran Q statistic ($P<0.1$) and quantified with the I^2 statistic, which describes the variation of effect size that is attributed to heterogeneity across studies. I^2 value greater than 50% indicates significant heterogeneity. The value of I^2 statistic is applied to select the appropriate

Table 1. Characteristics of included studies

NO.	Author	Combination therapy group					Teriparatide group				
		Number	Age (mean ± SD)	Body mass index (kg/m^2)	History of fragility fracture (no, %)	Dosages and methods	Number	Age (mean ± SD)	Body mass index (kg/m^2)	History of fragility fracture (no, %)	Dosages and methods
1	Tsai 2015	30	66±9	25.4±4.9	10 (33%)	Teriparatide 20 ug daily, denosumab 60 mg every 6 months	31	66±8	25.5±3.8	16 (52%)	Teriparatide 20 ug daily
2	Leder 2015	23	65.3±8.0	25.9±5.2	8 (35%)	24 months of teriparatide (20 μg daily), denosumab (60 mg every 6 months), 24 months of denosumab	27	66.1±7.9)	25.5±3.7	14 (52%)	24 months of teriparatide (20 ug daily), 24 months of denosumab
3	Leder 2014	30	65.9±9.0	25.4±4.9	10 (33)	Teriparatide (20 μg daily), denosumab (60 mg every 6 months) for 24 months	31	65.5±7.9	25.5±3.8	16 (52)	Teriparatide (20 ug daily) for 24 months
4	Tsai 2013	30	65.9±9.0	25·4±4·9	10 (33%)	Teriparatide (20 μg daily), denosumab (60 mg every 6 months)	31	65.5±7.9	25.5±3.8	16 (52%)	Teriparatide (20 ug daily)

Table 2. Quality assessment of included studies

NO.	Included studies	Type of study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed
1	Tsai 2015	RCT	Y	Y	Y	N
2	Leder 2015	RCT	Y	Y	Y	N
3	Leder 2014	RCT	Y	Y	Y	N
4	Tsai 2013	RCT	Y	Y	Y	N

RCT: randomized controlled trial, Y: yes, N: no.

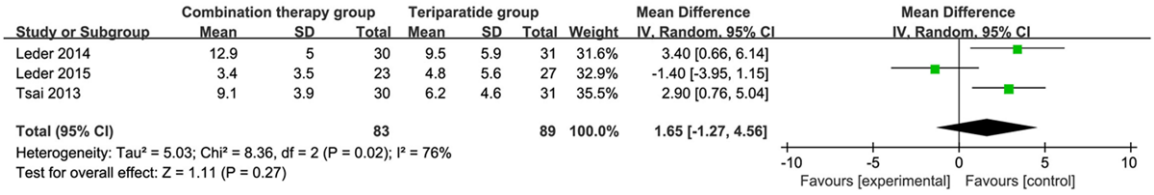

Figure 2. Forest plot for the meta-analysis of spine BMD (%).

pooling method: the fixed-effect model is used for I^2<50% and the random-effect model is selected for I^2>50%. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias is not assessed. P<0.05 in two-tailed tests is considered statistically significant. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Description of studies and quality assessment

Figure 1 shows the search strategy and selection process of this meta-analysis. In all, 965 studies in the first search are potentially relevant. 307 duplicates are removed. A total of 658 studies are excluded (irrelevant subjects) based on the initial screening of the titles and/or abstracts. And 3 articles are removed for the subjects not being RCT or CCT. The remaining 4 articles are included in this meta-analysis [18, 20, 21, 24].

Table 1 demonstrates the characteristics of the included studies. Four trials are all RCTs [18, 20, 21, 24]. In three included trials, teriparatide (20 μg daily) and denosumab (60 mg every 6 months) are used in combination therapy group, and teriparatide (20 μg daily) is applied in the teriparatide group [18, 21, 24], but in another trial, patients in combination therapy group obtain 24 months of teriparatide (20 μg daily) and denosumab (60 mg every 6 months), as well as subsequent 24 months of denosumab, while patients in teriparatide group get 24 months of teriparatide (20 μg daily) and subsequent 24 months of denosumab [20]. After contacting the authors, "Adequate sequence generation", "Allocation concealment" and "Blinding" are all "yes" in all articles (**Table 2**) [18, 20, 21, 24].

Primary outcome: spine BMD and hip BMD

These two outcome data are analyzed with a random-effect model, and the pooled estimate of three included RCTs suggest that combination treatment cannot significantly improve spine BMD compared to teriparatide treatment (mean difference = 1.65%; 95% CI = -1.27% to 4.56%; P = 0.27), with significant heterogeneity among the studies (I^2 = 76%, heterogeneity P = 0.02) (**Figure 2**).

However, combination treatment is found to significantly increase hip BMD than teriparatide treatment (mean difference = 3.59%; 95% CI = 2.23% to 4.95%; P<0.00001), but with significant heterogeneity among the studies (I^2 = 59%, heterogeneity P = 0.09) (**Figure 3**).

Sensitivity analysis

Significant heterogeneity is observed among the included studies for the primary outcome (I^2 = 76% for spine BMD and I^2 = 59% for hip BMD).

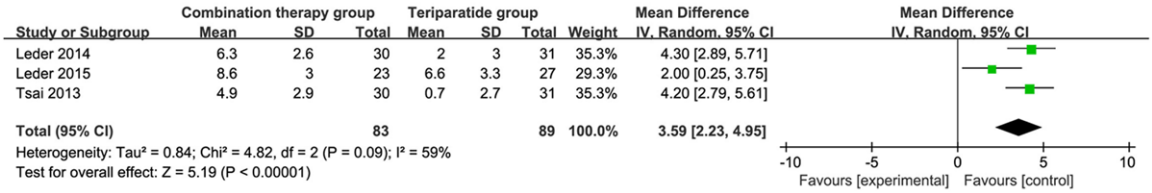

Figure 3. Forest plot for the meta-analysis of hip BMD (%).

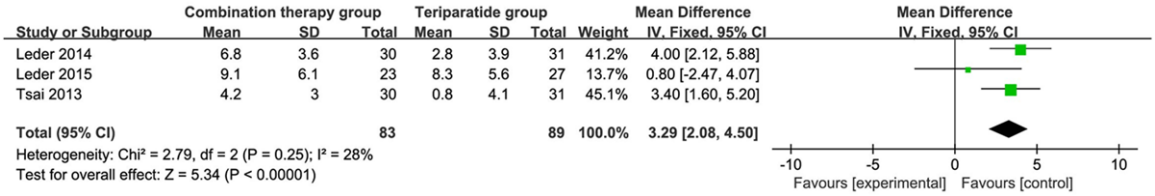

Figure 4. Forest plot for the meta-analysis of femoral neck BMD (%).

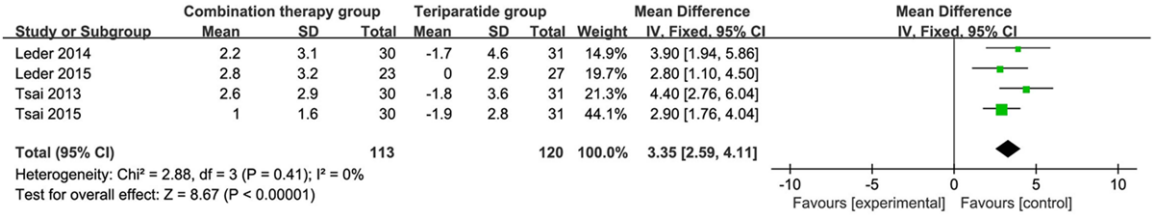

Figure 5. Forest plot for the meta-analysis of radius BMD (%).

As shown in **Figures 2** and **3**, the study conducted by Leder [20] shows the results that are almost completely out of range of the others and probably contribute to the heterogeneity. After excluding this study, the results indicate that compared with teriparatide treatment, combination treatment is associated with a significant improvement in spine BMD (mean difference = 3.09%; 95% CI = 1.40% to 4.77%; P = 0.0003) and hip BMD (mean difference = 4.25%; 95% CI = 3.25% to 5.25%; P<0.00001). No heterogeneity is observed among the remaining studies (I^2 = 0%) for both outcome data.

Secondary outcome

Compared with teriparatide treatment, combination treatment significantly improves femoral neck BMD (mean difference = 3.29%; 95% CI = 2.08% to 4.50%; P<0.00001; **Figure 4**) and radius BMD (mean difference = 3.35%; 95% CI = 2.59% to 4.11%; P<0.00001; **Figure 5**).

Adverse events

All four included studies report no drug-related serious adverse events [18, 20, 21, 24].

Publication bias

Publication bias was observed (P = 0.73) based on Begg's test and Egger's regression test.

Discussion

Previous studies reported that combination treatment using teriparatide and bisphosphonates showed no additive effects on improving the BMD of patients with osteoporosis [15, 16, 25], but combination therapy of teriparatide and denosumab was found to produce some additive efficacy to increase BMD and the results may be attributed to acute and sustained suppression of bone resorption [20].

Our meta-analysis suggests combination treatment of teriparatide and denosumab is associ-

ated with significantly improved BMD of hip, femoral neck, and radius, but there is no significant difference of spine BMD between combination treatment and teriparatide treatment. Regarding the sensitivity analysis, in one included study, patients obtained 24 months of teriparatide and denosumab, as well as subsequent 24 months of denosumab in the combination therapy group. Patients got 24 months of teriparatide and subsequent 24 months of denosumab in teriparatide group [20]. These may have some influence on the pooling results of combination treatment versus teriparatide treatment. After excluding this study, the results indicate that combination treatment can significantly increase spine BMD and hip BMD compared to teriparatide treatment, and there is no heterogeneity among the remaining studies (I^2 = 0%).

In that study [20], compared with patients in teriparatide treatment group, patients in the combination therapy group show significantly higher spine BMD in the first 24 months, but have reduced spine BMD in the second 24 months. These indicate that there may be some inhibition influence of denosumab on teriparatide treatment, but this inhibition acts at a late time. In addition, combination treatment of denosumab and teriparatide shows no important effect on trabecular thickness (Tb.Th) and trabecular number (Tb.N) than teriparatide treatment [21]. And more studies are required to explore these mechanisms.

Drug-related serious adverse events are not found in combination treatment group and teriparatide group, and these confirm the safety of denosumab and teriparatide treatment. The quality assessment shows that in general, these four included trials have relatively good quality. However, several limitations should be taken into account. Firstly, our analysis is based on only four RCTs and they have a relatively small sample size (n<100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. There is significant heterogeneity among the reviewed studies, possibly because of sample size, baseline characteristics of patients and study quality. Next, BMD is regarded as a reliable but imperfect predictor of antifracture efficacy, and there is lack of data regarding the incidence of fracture in patients receiving combination treatment. Finally, some unpublished and missing data may lead bias to the pooled effect.

Conclusions

Although various limitations exist, our meta-analysis clearly suggests that combination treatment of denosumab and teriparatide can effectively improve BMD of patients with osteoporosis. This combination treatment should be administrated to treat osteoporosis with caution. More trials with large sample sizes are required to confirm the influence of combination treatment on osteoporosis.

Disclosure of conflict of interest

None.

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