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Head-to-head comparisons of bisphosphonates and teriparatide in osteoporosis: a meta-analysis

Abstract

Purpose: This meta-analysis aimed to compare the efficacy and safety of teriparatide vs. bisphosphonates in the management of osteoporosis.

Methods: A total of 1,967 patients from eight randomized controlled trials were analyzed; outcomes included bone mineral density (BMD) of the femoral neck, total hip and lumbar spine, vertebral and nonvertebral fractures and any adverse event. A subgroup analysis of treatment effectiveness was performed according to the etiology of osteoporosis; i.e., glucocorticoid-induced osteoporosis (GIO) vs. post-menopausal osteoporosis (PO).

Results: Teriparatide increased the BMD of the lumbar spine, femoral neck and total hip to a greater extent than bisphosphonates. Patients treated with teriparatide also had a lower risk of vertebral fractures compared with bisphosphonates; however, no difference in risk of nonvertebral fractures (or adverse events) was found. GIO subgroups showed larger increases in BMD of the lumbar spine, total hip and femoral neck in patients treated with teriparatide compared with bisphosphonates. The PO subgroup showed larger increases in BMD of the lumbar spine in patients treated with teriparatide compared with bisphosphonates. Patients in the GIO subgroup (but not the PO subgroup) were less likely to suffer a vertebral fracture on teriparatide as compared with bisphosphonates. In contrast, no significant difference in the percentage of nonvertebral fractures was noted between the two types of treatment for either subgroup.

Conclusion: Teriparatide significantly increased the BMD of lumbar spine, total hip and femoral neck, particularly in GIO-induced osteoporosis. Teriparatide did not lower the risk of nonvertebral fractures when compared with bisphosphonates.

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Osteoporosis is a chronic disorder of the skeletal system characterized by compromised bone strength [1]. Current estimates suggest that approximately 30% of women and 19% of men in the United States and Europe are at risk for osteoporosis, and that an estimated 9 million fractures associated with osteoporosis occur annually [1]. Approximately 30% of women with osteoporosis have sustained at least one vertebral fracture by the age of 75 years [2], resulting in pain, disability and compromised quality of life [1]. Although osteoporosis is best known as an affliction of postmenopausal women, a variety of additional patient populations are also at risk, including men, the very elderly or disabled, patients on long-term glucocorticoid therapy (e.g., patients with asthma, rheumatoid arthritis and systemic lupus erythematosus) and patients with either renal disease or who are post-transplantation [1, 3].

Glucocorticoid-induced osteoporosis (GIO) is the third most-common etiology of pathological bone loss (behind post-menopausal osteoporosis [PO] and bone loss due to aging), approaching 20% of all patients with osteoporosis [4]. As has been shown in numerous mouse models of GIO, an early phase of exaggerated osteoclast-mediated bone resorption is followed by a chronic phase of decreased osteoblastogenesis and reduced bone formation [4-6]. In contrast, estrogen deficiency-induced bone loss in PO has little effect on the osteoblast, being primarily associated with enhanced osteoclast formation and activity and reduced osteoclast apoptosis, resulting in large increases in bone resorption [7-10].

Medical treatment options have improved in recent years and now include drugs from several classes and with various mechanisms of action. In addition, treatment guidelines have been published by various organizations [11]. Such options include the bisphosphonates, selective estrogen receptor modulators, estrogen, denosumab (antibody against RANKL) and parathyroid hormone analogues. The latter include teriparatide, a recombinant human parathyroid hormone [rhPTH(1-34)] [3]. The mechanism underlying GIO favors PTH analogue therapy because chronic glucocorticoid use is primarily characterized by changes in osteoblast maturation, activity and survival [4].

Currently, bisphosphonates are considered the first-line treatment option in patients with osteoporosis, according to various studies and global organizations [12]. Bisphosphonates inhibit osteoclast-mediated bone resorption, whereas teriparatide is a parathyroid hormone analog with anabolic activity [13]. More specifically, teriparatide directly stimulates bone formation [14]. Teriparatide induces differentiation of pre-osteoblasts into osteoblasts, stimulates preexisting

osteoblasts to form new bone and decreases osteoblast apoptosis [3, 15-17]. Because a primary action of glucocorticoids is to decrease bone formation, the bone anabolic effects of teriparatide may directly target key pathogenic mechanisms associated with long-term glucocorticoid therapy [3].

Despite the availability of various medications, many patients remain poorly treated [1]. Persistent roadblocks to adequate treatment of osteoporosis include paucity of data in specific patient populations, poor management of patients' concerns regarding adverse effects and lack of adherence to therapy [1].

The purpose of this meta-analysis was to compare the efficacy and safety of teriparatide with bisphosphonates to help advance the treatment of patients with osteoporosis. In particular, a subgroup analysis of treatment effectiveness was performed according to the etiology of osteoporosis; i.e., PO vs. GIO.

Materials and Methods

Inclusion and exclusion criteria

A computerized search of EMBASE, PubMed and Cochrane databases from inception until May 4, 2016 was performed using combinations of the following terms: (alendronate OR risedronate OR bisphosphonate) AND (teriparatide OR parathyroid hormone) AND (osteoporosis) AND (bone density) AND (randomized). Articles were included if they were randomized controlled trials (RCTs), included patients with osteoporosis (PO or GIO) and the intervention directly compared the bone mineral density (BMD) or fracture outcomes of teriparatide and bisphosphonates. Articles were excluded if they were any other type of publication (e.g., retrospective study, letters, comments, editorials and case reports) or were non-English publications. Studies were also excluded if they involved full-length parathyroid hormone (1-84) or combination treatments. Studies were excluded if they involved patients with osteoporosis but no data of subgroups of PO or GIO could be extracted.

Data extraction and quality assessment

Two independent reviewers extracted data from the eligible studies. A third reviewer was consulted for resolution of any disagreement. The quality of the included studies was assessed based on the Cochrane validation of assessment of eligible trials [18].

FIGURE 1. (A) Flow diagram of study selection. (B) Quality assessment.

Outcome measures

Primary efficacy measures included mean changes from baseline (%) of lumbar spine BMD, total hip BMD and femoral neck BMD, the risk of vertebral fractures and the risk of nonvertebral fractures. When reported, adverse events were also compared.

Statistical analysis

Odds ratios with 95% confidence intervals (CIs) were calculated for dichotomous outcomes (risk of vertebral and nonvertebral fractures and any adverse events) between patients treated with teriparatide and a bisphosphonate, for each individual study and for all the studies combined. A standardized mean difference (SMD) (with 95% CIs between the two groups) was calculated for continuous outcomes (changes from baseline of lumbar spine BMD, total hip BMD and femoral neck BMD). A χ^2 -based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. Heterogeneity determined using the I^2 statistic was defined as follows: 0 to 24% = no heterogeneity;

25 to 49% = moderate heterogeneity; 50 to 74% = large heterogeneity; and 75 to 100% = extreme heterogeneity. Because the number of studies included in the meta-analysis was small, heterogeneity tests had low statistical power [19]. When tests for heterogeneity are underpowered, random-effects models of analysis are routinely used [20]. The National Research Council report recommends the use of random-effects approaches for meta-analysis and for the exploration of sources of variation in study results [21].

In addition, planned subgroup analysis of treatment effectiveness was performed according to the etiology of osteoporosis; i.e., PO vs. GIO. For each of the meta-analyses, the leave-one-out approach was used to evaluate the effect of individual studies on the pooled results. Publication bias analysis was not performed because the number of studies was too few to detect an asymmetric funnel. A P value <0.05 was considered statistically significant. The homogeneity test, pooled estimates and sensitivity analysis were performed using a commercial software package (Comprehensive Meta-Analysis, version 2.0; Biostat, Englewood, NJ, USA).

Results

As shown in Figure 1A, of the 175 studies originally identified and screened, eight studies [3, 12, 22-27] were included in the meta-analysis. Of those, two studies included patients with GIO, and the remaining six involved patients with PO (Table 1). All eight studies directly compared the efficacy of teriparatide and a bisphosphonate (risedronate, alendronate or zoledronic acid), and the follow-up period ranged from 12 to 36 months (Table 1). These eight RCTs evaluated 1,967 subjects (average number of subjects, 243; median, 175; range, 44–710) and average patient age ranged from 55.1 to 71.6 years. Additional study details regarding patient demographics, treatments, follow-up periods, outcome measures and any adverse event have been described in detail in Tables 1 and 2.

Bone mineral density

All BMD results are shown in Figure 2. Eight studies reported the mean change in lumbar spine BMD. There was large heterogeneity (Q statistic = 19.089, I^2 = 63.33%) observed among the studies (Figure 2A). The result of the meta-analysis showed that patients treated with teriparatide had a larger increase in lumbar spine BMD compared with those treated with bisphosphonates, with a pooled SMD of 0.63 (95% CI: 0.46 to 0.80, P < 0.001).

The subgroup analysis results showed that in the GIO patient subgroup (n = 2), patients treated with teriparatide had a larger increase in lumbar spine BMD compared with those treated with bisphosphonates (pooled SMD = 0.66, 95% CI: 0.43 to 0.90, P < 0.001). Moreover, patients in the PO subgroup (n = 6) treated with teriparatide demonstrated a

TABLE 1. Summary of patient characteristics from the included studies

First author (year)	Study design	Type of subjects	Interventions	Number of subjects	Age (year), mean (SD)	Gender (F/M)	Time of final visit (months)
Glüer (2013)	Open label RCT	GIO in men	Teriparatide	45	57.5 (12.8)	0/45	18
			Risedronate	47	55.1 (15.5)	0/47	
Hadji (2012)	Double blind RCT	Women $\geq$ 45 years of age and at least 2 years post-menopausal PO	Teriparatide	360	70.5 (8.8)	360/0	18
			Risedronate	350	71.6 (8.1)	350/0	
Cosman (2011)	Partial double-blinded RCT	Postmenopausal women PO	Teriparatide	138	63.8 (9.1)	138/0	12
			Zoledronic acid	137	66.1 (9.0)	137/0	
Finkelstein (2010)	Unblinded RCT	Postmenopausal women PO	Teriparatide	20	65 (7)	20/0	30
			Alendronate	29	64 (6)	29/0	
			Both	20	62 (7)	20/0	
Saag (2009)	Double blind RCT ^a	277 postmenopausal women, 68 pre-menopausal women, 83 men GIO	Teriparatide	214	56.1 (13.4)	172/42	36
			Alendronate	214	57.3 (14.0)	173/41	
Anastasilakis (2008)	Open label RCT	Postmenopausal women PO	Teriparatide	22	65.4 (SE: 1.6)	22/0	12
			Risedronate	22	64.7 (SE: 1.5)	22/0	
McClung (2005)	Double-blind RCT	Postmenopausal women PO	Teriparatide	102	65.3 (SE 8.4)	0/203	18
			Alendronate	101	66.6 (SE 8.5)		
Body (2002)	Double-blind RCT	Postmenopausal women PO	Teriparatide	73	66 (8)	146/0	12
			Alendronate	73	65 (9)		

Abbreviations: GIO, glucocorticoid-induced osteoporosis; PO, postmenopausal osteoporosis; SD, standard deviation; SE, standard error; RCT, randomized controlled trial

TABLE 2. Summary of study outcomes

First author (year)	Interventions	Mean percent change from baseline			Risk of vertebral fracture, n (%)	Risk of nonvertebral fracture, n (%)	Any AEs, n (%)
		Lumbar spine BMD	Total hip BMD	Femoral neck BMD			
Glüer (2013)	Teriparatide	6.94%	2.07%	1.52%	NR	0	25 (55.6%)
	Risedronate	3.33%	0.99%	-1.10%	NR	5 (10.6%)	35 (74.5%)
Hadji (2012)	Teriparatide	7.80%	2.05%	2.11%	16 (4.4%)	28 (7.8%)	285 (79.2%)
	Risedronate	2.63%	0.83%	0.77%	33 (9.4%)	29 (8.3%)	285 (81.4%)
Cosman (2011)	Teriparatide	7%	1.1%	0.1%	1 (0.7%)	7 (5.1%)	118 (85.4%)
	Zoledronic acid	4.3%	2.2%	1.8%	5 (3.6%)	8 (5.8%)	125 (91.2%)
Finkelstein (2010)	Teriparatide	17.80%	8.10%	10.80%	NR	NR	NR
	Alendronate	6.80%	3.10%	3.50%	NR	NR	NR
Saag (2009)	Teriparatide	11.00%	5.20%	6.30%	3 (1.7%)	25 (14.5%)	194 (91%)
	Alendronate	5.30%	2.70%	3.40%	17 (10.1%)	20 (11.8%)	184 (86%)
Anastasilakis (2008)	Teriparatide	0.045*	NR	NR	NR	NR	11 (39.1%)
	Risedronate	0.025*	NR	NR	NR	NR	7 (33.3%)
McClung (2005)	Teriparatide	10.30%	NR	3.90%	9 (8.9%)	NR	NR
	Alendronate	5.50%	NR	3.50%	8 (7.9%)	NR	NR
Body (2002)	Teriparatide	14.10%	4.80%	4.20%	3 (4.1%)	NR	NR
	Alendronate	5.90%	2.40%	1.20%	10 (3.7%)	NR	NR

Abbreviations: BMD, bone mineral density; NR, not reported

*Mean change from baseline

larger increase in lumbar spine BMD compared with those treated with bisphosphonates (pooled SMD = 0.60, 95% CI: 0.35 to 0.81, $P < 0.001$).

Six studies reported the mean change in total hip BMD (Figure 2B). Large heterogeneity among the studies was detected (Q statistic = 18.854, $I^2 = 73.48\%$; Figure 2B). The results showed that patients treated with teriparatide had a greater increase in total hip BMD compared with those treated with bisphosphonates (pooled SMD = 0.29, 95% CI: 0.13 to 0.45, $P = 0.001$; Figure 2B). In addition, patients in the GIO subgroup ($n = 2$) treated with teriparatide showed a larger increase in total hip BMD compared with those treated with bisphosphonates (pooled SMD = 0.30, 95% CI: 0.11 to 0.48, $P = 0.002$). In the PO subgroup ($n = 4$), there was no significant difference in total hip BMD between the two treatments (pooled SMD = 0.26, 95% CI: -0.09 to 0.60, $P = 0.140$).

Seven studies reported the mean change in femoral neck BMD (Figure 2C). Extreme heterogeneity was observed among the studies (Q statistic = 30.676, $I^2 = 80.44\%$). The overall analysis revealed patients treated with teriparatide had a larger increase in femoral neck BMD compared with those treated with bisphosphonates (pooled SMD = 0.37, 95% CI: 0.18 to 0.56, $P < 0.001$; Figure 2C). Patients in the GIO subgroup ($n = 2$) treated with teriparatide showed a larger increase in femoral neck BMD compared with those treated with bisphosphonates (pooled SMD = 0.41, 95% CI: 0.17 to 0.64, $P = 0.001$; Figure 2C). In the PO subgroup ($n = 5$), there was no significant difference in femoral neck BMD between the two groups (pooled SMD = 0.29, 95% CI: -0.04 to 0.61, $P = 0.085$).

A. Lumbar spine BMD

B. Total hip BMD

C. Femoral BMD

FIGURE 2. . Subgroup analysis of post-menopausal osteoporosis (PO) vs. glucocorticoid-induced osteoporosis (GIO) for (A) lumbar spine BMD, (B) total hip BMD and (C) femoral neck BMD.

Fractures

Five studies reported the percentage of vertebral fractures (Table 2, Figure 3A). Moderate heterogeneity was observed among the studies (Q statistic = 7.087, I^2 = 43.56%; Figure 3A). Patients treated with teriparatide were less likely to suffer vertebral fractures compared with those treated with bisphosphonates (pooled odds ratio [OR] = 2.57, 95% CI: 1.46 to 4.54, P = 0.001). Only Saag et al. [3] reported the risk of vertebral fractures in the GIO subgroup, and they indicated patients treated with teriparatide were less likely to suffer vertebral fractures compared with those treated with bisphosphonates (OR = 6.34, 95% CI: 1.82 to 22.05, P = 0.004). In the PO subgroup (n = 4), patients treated with

teriparatide were less likely to suffer vertebral fractures compared with those treated with bisphosphonates (pooled OR = 2.03, 95% CI: 1.07 to 3.84, P = 0.030; Figure 3A)

Four studies reported the percentage of nonvertebral fractures and no heterogeneity was observed among the studies (Figure 3B). The risk of nonvertebral fractures did not differ between the two treatment groups (pooled OR = 1.11, 95% CI: 0.69 to 1.79, P = 0.654; Figure 3B). Analysis of patients in GIO subgroup (n = 2) revealed no significant difference in the percentage of nonvertebral fractures between the two treatments (OR = 2.06, 95% CI: 0.16 to 25.81, P = 0.574; Figure 3B). In the PO subgroup (n = 2) there was no significant difference in nonvertebral fractures between the

A. Vertebral fracture

B. Nonvertebral fracture

FIGURE 3. Subgroup analysis of post-menopausal osteoporosis (PO) vs. glucocorticoid-induced osteoporosis (GIO) for (A) vertebral fracture, (B) nonvertebral fracture and (C) any adverse event.

TABLE 3. Sensitivity analysis

First author (year)	Statistics with study removed				
Lumbar spine BMD	Points	Lower limit	Upper limit	Z-Value	P-Value
Glüer (2013)	0.61	0.40	0.82	5.75	<0.001
Hadji (2012)	0.66	0.47	0.84	7.02	<0.001
Cosman (2011)	0.60	0.36	0.84	4.86	<0.001
Finkelstein (2010)	0.55	0.38	0.72	6.45	<0.001
Saag (2009)	0.59	0.36	0.81	5.16	<0.001
Anastasilakis (2008)	0.63	0.43	0.83	6.28	<0.001
McClung (2005)	0.63	0.41	0.85	5.68	<0.001
Body (2002)	0.55	0.36	0.74	5.60	<0.001
Total hip BMD					
Glüer (2013)	0.25	0.00	0.50	1.94	0.052
Hadji (2012)	0.30	-0.02	0.62	1.85	0.065
Cosman (2011)	0.32	0.15	0.50	3.55	0.000
Finkelstein (2010)	0.18	-0.02	0.39	1.73	0.083
Saag (2009)	0.26	-0.04	0.56	1.71	0.088
Body (2002)	0.22	-0.04	0.47	1.66	0.097
Femoral neck BMD					
Glüer (2013)	0.29	0.02	0.56	2.092	0.036
Hadji (2012)	0.38	0.04	0.72	2.166	0.030
Cosman (2011)	0.40	0.15	0.65	3.171	0.002
Finkelstein (2010)	0.21	0.00	0.41	1.989	0.047
Saag (2009)	0.33	0.03	0.63	2.12	0.034
McClung (2005)	0.39	0.09	0.69	2.535	0.011
Body (2002)	0.31	0.02	0.59	2.094	0.036
Vertebral fracture					
Hadji (2012)	2.87	1.02	8.09	1.99	0.047
Cosman (2011)	2.40	1.14	5.02	2.32	0.021
Saag (2009)	2.03	1.07	3.84	2.18	0.030
McClung (2005)	2.96	1.80	4.86	4.28	<0.001
Body (2002)	2.40	1.06	5.40	2.11	0.035
Nonvertebral fracture					
Glüer (2013)	0.97	0.66	1.42	-0.15	0.877
Hadji (2012)	1.11	0.48	2.57	0.25	0.800
Cosman (2011)	1.03	0.56	1.90	0.11	0.914
Saag (2009)	1.22	0.65	2.29	0.62	0.536
Adverse events					
Glüer (2013)	0.96	0.60	1.56	-0.15	0.881
Hadji (2012)	1.09	0.52	2.26	0.22	0.827
Cosman (2011)	0.99	0.57	1.73	-0.04	0.971
Saag (2009)	1.32	0.81	2.15	1.10	0.273
Anastasilakis (2008)	1.22	0.75	2.00	0.81	0.417

two treatments (OR = 1.09, 95% CI: 0.67 to 1.76, $P=0.726$; Figure 3B).

Adverse events

Five studies reported the percentage of any adverse event (Figure 3C). Large heterogeneity was observed among the studies (Q statistic = 9.502, $I^2 = 57.90\%$). The overall analysis revealed the risk of any adverse event did not significantly differ between the two treatments (pooled OR = 1.15, 95% CI: 0.71 to 1.85, $P=0.570$; Figure 3C). Adverse events reported for bisphosphonates and teriparatide were similar, and included both treatment-emergent and serious adverse events such as peripheral edema, arthralgia, dyspnea, nausea, weight gain, intervertebral disc protrusion, exacerbation of Crohn's disease and falls.

Sensitivity

Sensitivity analyses of BMD, vertebral fractures, nonvertebral fractures, and any adverse event were performed using the leave-one-out approach (Table 3). With the exception of total hip BMD, the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating that the meta-analysis data was robust and not overly influenced by any one study. For total hip BMD, the results differed when the studies by Glüer *et al.* [22], Hadji *et al.* [23], Finkelstein *et al.* [12], Saag *et al.* [3] and Body *et al.* [27] were removed; the pooled effect size became non-significant, suggesting these studies may have overly influenced the findings. However, the P values were borderline, indicating no obvious influence of any individual study on the pooled estimate.

Discussion

This meta-analysis of 1,967 patients from eight RCTs showed that patients treated with teriparatide had a larger increase in lumbar spine BMD compared with those treated with bisphosphonates. Patients treated with teriparatide also showed a larger increase in total hip BMD and femoral neck BMD compared with those treated with bisphosphonates. Patients treated with teriparatide also had a lower risk of vertebral fracture compared with bisphosphonates; however, no difference in risk of nonvertebral fractures or adverse events was found between the two treatments.

Subgroup analysis was also performed to differentiate between the two main types of osteoporosis. GIO subgroups showed larger increases in BMD of the lumbar spine, total hip and femoral neck in patients treated with teriparatide

compared with bisphosphonates. In the PO subgroup, larger increases in BMD of the lumbar spine were noted; however, there was no significant difference in BMD of the total hip and femoral neck in patients treated with teriparatide compared with bisphosphonates. Patients in the GIO subgroup, but not in the PO subgroup, were less likely to suffer a vertebral fracture on teriparatide as compared with bisphosphonates, but this result was based on only one study, that of Saag *et al.* [3]. In contrast, no significant difference in percentage of nonvertebral fractures was noted between the two types of treatment for either subgroup. The current study showed that teriparatide is more effective than bisphosphonates in improving BMD of the lumbar spine, total hip and femoral neck, particularly in GIO-induced osteoporosis, and herein lies the novelty of the results from the current meta-analysis.

Other meta-analyses have been conducted to evaluate the various drugs used to treat osteoporosis. Nevitt *et al.* [28] found that patients treated with teriparatide had a reduced risk of back pain (either new or worsening back pain) compared with patients treated with alendronate. Additional outcome measures, such as fracture, BMD or markers of bone turnover, were not included as endpoints in that meta-analysis, and could not be directly compared with the current meta-analysis. Similarly, Murad *et al.* [29] compared the effect of teriparatide vs. other agents in the treatment of osteoporosis, including several bisphosphonates. In that study, teriparatide had the highest risk reduction regarding fractures of the hip, vertebral body and nonvertebral fractures, and was ranked first for efficacy compared with the other drugs studied. In our study, patients treated with teriparatide were also less likely to suffer a nonvertebral fracture compared with those treated with bisphosphonates, although the trend failed to reach significance. The discrepancy in results between our study and that of Murad *et al.* [29] may be due to differences in methodology (we compared two treatments directly whereas Murad *et al.* [29] compared two treatments indirectly). In addition, we did not differentiate between the type of bisphosphonate used, whereas Murad *et al.* did [29]. Murad *et al.* concluded that teriparatide, bisphosphonates and denosumab were most effective in reducing risk of fragility fractures, and that differences in efficacy among those drugs were small. According to Murad *et al.* [29], the choice of drug for managing osteoporosis should be based on cost and safety. Zhang *et al.* [30] performed meta-analysis indirectly comparing teriparatide, denosumab and bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women. Different treatments were found to have different efficacies for different types of fractures, but

overall the results showed that teriparatide, denosumab, alendronate and risedronate were all effective in reducing the risk of vertebral and nonvertebral fractures, denosumab, alendronate and risedronate also reduced the risk of hip fractures, and risedronate also reduced the risk of upper-arm fractures. Freemantle *et al.* [31] used network meta-analysis to perform an indirect and mixed treatment comparison of the efficacy of osteoporosis treatments for preventing fracture. The analysis used data from 33 studies and found that all treatments except etidronate significantly reduced risk of new vertebral fractures compared with placebo, denosumab, risedronate and zoledronic acid significantly reduced nonvertebral and hip fractures, and alendronate, strontium ranelate, and teriparatide significantly reduced risk for non-vertebral fractures. The mixed treatment comparison analysis showed that denosumab was more effective than strontium ranelate, raloxifene, alendronate and risedronate in preventing new vertebral fractures. Finally, in a meta-analysis involving only postmenopausal women, Han and Wan [32] found that teriparatide significantly increased spine and hip BMD, although the improvement was deemed conservative due to statistical heterogeneity.

In the current study, sensitivity analyses of BMD, vertebral fractures, nonvertebral fractures and adverse events were performed using the leave-one-out approach. With the exception of total hip BMD, adverse events and risk of vertebral fracture, the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating that the meta-analysis data was robust and not overly influenced by any one study. For the total hip BMD, however, the results differed when the studies by Glüer *et al.* [22], Hadji *et al.* [23], Finkelstein *et al.* [12], Saag *et al.* [3] and Body *et al.* [27] were individually removed; the pooled effect size became non-significant, suggesting these studies may have overly influenced the findings. The P values with these studies removed were borderline, indicating no obvious influence of any individual study on the pooled estimate. The heterogeneity observed may also be due to the different types of bisphosphonates used among the included studies (only Hadji *et al.* [23] used risedronate and Cosman *et al.* [25] used zoledronic acid), or selection bias or bias from intent-to-treat analysis in the three studies which evaluated vertebral fractures (McClung *et al.* [24], Saag *et al.* [3] and Body *et al.* [27]).

Together, the current meta-analysis and previously published analyses suggest the superiority of teriparatide over bisphosphonates in the management of osteoporosis, based primarily on fracture occurrence and BMD. It should be noted, however, that in most countries there is a limitation to

the duration of teriparatide therapy; e.g., in the United States and Canada, lifetime exposure is limited to 2 years [33]. Furthermore, the reduction of fracture risk appears to be related to duration of continuous therapy, and thus shorter treatment regimens may not produce the same effect as a single course 24 months long [33]. This is in contrast to treatment with bisphosphonates, for which there is no limitation on the duration of therapy.

An additional potential outcome to consider in futures studies is quality of life (QOL). Panico *et al.* [2] demonstrated that teriparatide improved QOL more than bisphosphonates based on the European Foundation for Osteoporosis.

The current study was a direct head-to-head comparison of two treatment methods. This type of analysis can be considered to be either a strength or a weakness of the study. A low risk of bias is the strength of a direct comparison; however, the sample size for such a study will be smaller than that examining a number of treatment options. A mixed-treatment comparison will obviously allow examination and comparison of multiple treatment options; however, this type of study will be limited by heterogeneity and variation among study parameters. For our study, we chose to do a head-to-head comparison to add information to the literature that is not already present, to provide further data for clinical decision making. As mentioned in the discussion of the study by Freemantle *et al.* [31], network meta-analysis can compile and compare all evidence on a particular topic regardless of study type, but it is limited by using direct and indirect comparisons and inevitable heterogeneity [34].

The current study had several limitations. The small number of studies in each group meant that the heterogeneity tests had low statistical power. We did not differentiate between the effects of different bisphosphonates (*i.e.*, alendronate *vs.* risedronate *vs.* zoledronic acid). In addition, the follow-up period varied among the studies: Finkelstein *et al.* [12] and Saag *et al.* [3] had longer durations of treatment than the other included studies. Although subgroup analyses based on treatment period or male gender were not possible due to the small number of patients in each study, Han and Wan [32] suggested that long-term treatment did not appear to contribute to differences in responsiveness to teriparatide. Further studies comparing short-term and long-term effects of teriparatide *vs.* bisphosphonates are warranted.

In conclusion, teriparatide significantly increased the BMD of lumbar spine, total hip and femoral neck, particularly in GIO-induced osteoporosis. Teriparatide did not lower the risk of nonvertebral fractures when compared with bisphosphonates. More studies evaluating safety and

treatment holidays are needed, as well as studies examining combination therapies.

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