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Efficacy of intravenous zoledronic acid in the prevention and treatment of osteoporosis: A meta-analysis

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ABSTRACT

Objective: To compare the effect of zoledronic acid in treatment and prevention of osteoporosis with placebo. **Methods:** Random control trials regarding zoledronic acid in treatment of osteoporosis were retrieved by selecting Medline, EMbase and Pubmed databases till April 2012. The RevMan software was used for all of the statistical analysis. **Results:** A total of 9 trials were included in this meta-analysis. The pooled effect showed that zoledronic acid could increase the bone mineral density by 2.98 times compared with placebo, and reduce the rate of fracture in patients by 32%. The results should the zoledronic acid intervention had significantly less serious adverse events than controls, and the odds ratio was 0.81 (0.76-0.87). The longer term intervention, more than 12 months intervention, could gain a better prevention effect for osteoporosis (*OR*, 95% *CI* for BMD was 3.35, 2.77-3.92; for fracture was 0.67, 0.54-0.82). **Conclusions:** This present study shows that zoledronic acid could be effective approach in the prevention of osteoporosis, and could increase the bone mineral density and reduce the risk of facture.

1. Introduction

Osteoporosis is a major health problem, the prevalence of osteoporosis increases with age. Overall, it is estimated that 50% of women and 25% of men aged more than 50 years will have osteoporosis-related fracture in their remaining lifetime[1]. Due to aging population in the world, the osteoporosis-related fractures have been a great problem in the world[2,3]. According to the World Health Organization data, osteoporosis affects approximately 75 million people throughout Europe, the US, and Japan[1]. In the US osteoporosis occurs in 55% of the population aged 50 years and above[2]. It is estimated that the number of women and men with osteoporosis would increase from 44 million to more than 61 million by 2020 in the America and the annual fractures and associated costs in the United States will increase by nearly 50%[2]. Likewise, worldwide projections of the incidence of hip fracture indicate that it will increase by 240% in women and 310% in men between 1990 and 2050[4]. The primary health burden imposed by osteoporosis is increased risk for bone fractures and the health cost. Fractures are usually associated with disability, reduced quality of life, increased risk of subsequent fractures, and also are related to higher mortality and high health care costs[2,3].

Oral nitrogen-containing bisphosphonates are standard treatment for osteoporosis[5], which could inhibit farnesyl diphosphate synthase, a key branch point of the mevalonate pathway, and inhibit protein prenylation in osteoclasts[6]. These nitrogen-containing bisphosphonates could induce bisphosphonates potent inhibitors of bone resorption and remodeling activity[7]. Zoledronic acid (ZOL) is an intravenous, nitrogen-containing bisphosphonate with

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a prolonged dosing interval and the potential to increase patient compliance with bisphosphonate therapy and thereby to improve patient outcomes. ZOL 5 mg has been approved by the Food and Drug Administration for the treatment of postmenopausal osteoporosis, treatment of male osteoporosis, and treatment and prevention of glucocorticoid-induced osteoporosis as a once-yearly infusion. It is also approved for prevention of osteoporosis in postmenopausal women as an infusion given once every 2 years[8]. However, the clinical evidence in the effect of ZOL on osteoporosis and its complication is conflicting. Therefore, we conducted a meta-analysis regarding the published randomized controlled clinical trials of ZOL in treatment and prevention of osteoporosis.

2. Materials and methods

2.1. Literature search

The Medline, EMbase and Pubmed were selected with the use of dozens of complex search strategies containing index terms. The data of the last search was April 2012. The best search strategy for each database that resulted in the most relevant randomized clinical trials was used in the final analysis (Figure 1). A total of 729 articles were identified, 9 randomized clinical trials regarding ZOL on osteoporosis were included finally.

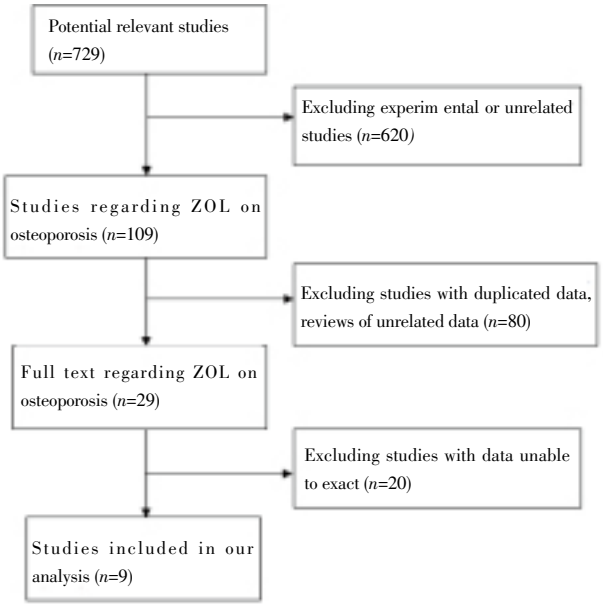

Figure 1. Flow chart of retrieving studies.

2.2. Study selection

Studies were included in our study were according to the following criteria: Firstly, the studies should be a comparison studies about ZOL supplements *vs*. placebo. Secondly, studies should report the clinical outcome of the effects of ZOL on the bone markers; Thirdly, the duplicated reports of the studies were excluded. Randomization by clusters or individuals were acceptable. We used no language or publication status restrictions.

Two researchers independently reviewed the title, abstract and conclusion of studies according to the inclusion and exclusion criteria of the relevant randomized clinical trials. If there was disagreement, consensus was resolved by discussion.

2.3. Data extraction

Data on year, county, study design, number of participants, intervention, and outcomes for bone markers were also independently extracted by two reviewers and were confirmed by each other. If necessary, data on outcomes for bone markers were obtained from graphs reported. If possible, we obtained necessary data which has not been reported by contacting the authors.

2.4. Statistical analysis

We performed a meta-analysis to determine the overall treatment effect of ZOL on bone markers, using RevMan software for all of the statistical analysis. The treatment effect of the included studies was estimated by the mean difference between the changes from baseline of bone marker to the makers after intervention. We used both a fixed effect model or a random effects model to calculate the weighted mean differences with 95% *CI*s for each comparison, a combined overall effect with *P* value, and the *P* value for testing heterogeneity ($P<0.1$ was considered significant). When there was significant heterogeneity across the included trials, a random effects model was used to analysis. The I^2 statistic was calculated by the percentage of I^2. 0% to 40% showed no heterogeneity; 30% to 60% showed moderate heterogeneity; 50% to 90% showed substantial heterogeneity; and 75% to 100% showed great heterogeneity across studies. Funnel plot was taken to evaluate publication bias. Subgroup analysis and meta-regressions were performed to investigate possible factors that might relate to varying effects of ZOL on each bone markers across trials, on the basis of menopausal status, ZOL and intervention duration.

3. Results

A total of 9 trials included in this meta-analysis (Table 1). Data for follow-up durations were ranged from 1 year to 6 years. In the included studies, participants in the comparison group had the similar demographics data with the control group. Most of the included studies were conducted in Western counties, only one study conducted in China. There were 8 studies regarding the outcome of bone mineral density (BMD), and 5 studies regarding the outcome of fracture. Most of the studies were conducted in female patients due to the high incidence of osteoporosis in females. The rate of serious adverse effect in ZOL intervention group was at the range of 20%-86%.

Figure 2 showed the effect of intravenous ZOL on the BMD among participants. The random effects model was used and revealed that the BMD among experimental participants was significantly higher than the controls. The pooled effect showed the ZOL could increase the BMD by 2.98 times compared with placebo, which indicated the ZOL could significantly increase the BMD among participants. Figure 3 showed that the role of ZOL in the fracture of participants. There was no significant heterogeneity among studies, and the I^2 was 29% (I^2=95%). All trials showed the ZOL could decrease the rate of fracture, and the pooled results showed the fracture in patients could be significantly reduced by 32%.

Moreover, analysis of the serious adverse effect of ZOL was shown in Figure 4. The results revealed the ZOL intervention had significantly less serious adverse effect than control, and the odds ratio was 0.81 (0.76-0.87). A significantly heterogeneity was found between studies. Most of the serious adverse effects were renal diseases, pyrexia and cardiovascular or cerebrovascular problems.

Subgroup analysis regarding the participants age and intervention duration time was also performed. Participants aged 50 years showed better effect of ZOL on osteoporosis, including higher BMD value and lower risk of fracture. Moreover, the longer term intervention, more than 12 months intervention, could gain a better prevention effect on osteoporosis (*OR*, 95% *CI* for BMD was 3.35, 2.77-3.92; for fracture was 0.67, 0.54-0.82) (Table 2 and Table 3). The funnel plots did not show an obvious publication bias (Figure 5 and Figure 6).

Table 1
Characteristics of the studies included in the meta-analysis.

Study ID	Country	Follow-up(months)	Samples (Intervention/ controls)	Age(years)	Sex	Outcomes	Adverse effect
Black 2012[9]	USA	36-72	451/470	75.5	Men & women	BMD, fracture	27.27% serious adverse effect in ZOL, 31.16% in control
Boonen 2011[10]	Belgium	12-24	250/248	72.6	Women	BMD, fracture	42.0% serious adverse effect in ZOL, 46.0% in control
Sambrook 2012[11]	USA	12	88/177	57.2	Women	BMD	No serious adverse effect
Boonen 2010[12]	Belgium	36	1 961/1 926	>75	Women	BMD, fracture	25.6% serious adverse effect in ZOL, 27.4% in control
Hwang 2011[13]	China	36	163/160	72.5±0.4	Women	BMD, fracture	20.2% serious adverse effect in ZOL, and 32.7% in control
Bubbear 2011[14]	The United Kingdom	12	7/7	28.6±14.4	9 men & 5 women	BMD	No serious adverse effect
Black 2007[15]	The United State	36	3 889/3 879	73.0±5.4	Women	BMD fracture	30.1% serious adverse effect in ZOL, and 29.2% in control
Kenneth 2007[16]	Holland	20	1 961/1 926	>50	24.5% men & 75.5% women	Fracture	38.3% serious adverse effect in ZOL, and 41.2% in control
Ian 2002[17]	New Zealand	12	59/59	45-80	Women	BMD	76% serious adverse effect in ZOL, and 86% in control

Study of subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV. Random. 95% CI
Balck 2012	1.49	0.21	451	0.95	0.18	470	13.0%	2.76 (2.58, 2.94)
Black 2007	1.36	0.14	3 889	0.79	0.14	3 879	13.1%	4.06 (3.98, 4.14)
Boonen 2010	4.98	0.98	1 961	1.98	0.54	1 926	13.1%	3.78 (3.68, 3.89)
Boonen 2011	2.70	0.34	250	1.90	0.23	248	12.9%	2.78 (2.50, 3.00)
Bubbear 2011	1.19	0.80	7	1.08	0.50	7	10.3%	0.15 (0.90, 1.20)
Hwang 2011	0.51	0.01	163	0.47	0.01	160	12.0%	7.58 (6.95, 8.21)
Ian 2002	0.95	0.10	59	0.88	0.08	59	12.7%	0.77 (0.39, 1.14)
Sambrook 2012	4.91	1.21	88	3.20	0.87	177	12.9%	1.71 (1.42, 2.01)
Total (95% CI)			**6 868**			**6 926**	**100.0%**	**2.98 (2.26, 3.71)**

Heterogeneity: Tau^2=1.03; Ch^2=842.78, df=7 (P<0.0001); I^2=99%

Test for overall effect: Z=8.12 (P<0.0001)

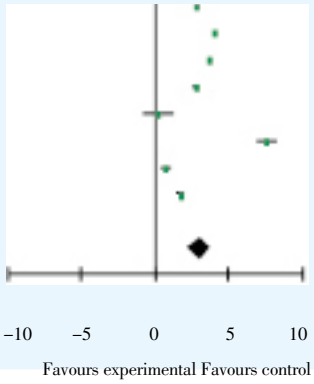

Figure 2. Effect of intravenous ZOL on the BMD.

Study of subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Balck 2012	14	451	27	470	5.7%	0.53 (0.27, 1.02)
Boonen 2010	50	1 961	70	1 926	15.4%	0.69 (0.48, 1.00)
Boonen 2011	92	1 062	139	1 065	23.2%	0.63 (0.48, 0.83)
Kenneth 2007	91	1 065	148	1 062	23.4%	0.58 (0.44, 0.76)
Black 2007	165	3 889	196	3 876	32.2%	0.83 (0.67, 1.03)
Total (95% CI)		**8 428**		**8 399**	**100.0%**	**0.68 (0.58, 0.80)**

Heterogeneity: Tau^2=0.01; Ch^2=5.64, df=4 (P=0.23); I^2=29%

Test for overall effect: Z=4.63 (P<0.0001)

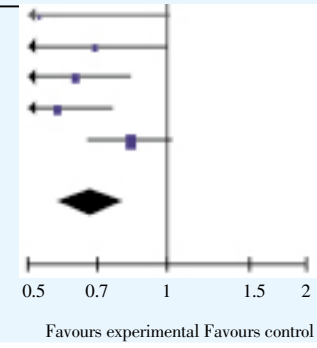

Figure 3. Effect of intravenous ZOL on the fracture.

Study of subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Balck 2012	123	451	146	470	5.2%	0.83 (0.63, 1.11)
Black 2007	1 171	3 889	1 133	3 879	39.3%	1.04 (0.95, 1.15)
Boonen 2010	502	1 961	528	1 926	19.6%	0.91 (0.79, 1.05)
Boonen 2011	105	250	114	248	3.3%	0.85 (0.60, 1.21)
Bubbear 2011	0	7	0	7		Not estimable
Hwang 2011	33	162	52	160	2.1%	0.53 (0.32, 0.88)
Ian 2002	45	59	51	59	0.6%	0.50 (0.19, 1.31)
Kenneth 2007	480	1 961	794	1 926	30.0%	0.46 (0.40, 0.53)
Sambrook 2012	0	88	0	177		Not estimable
Total (95% CI)		**8 828**		**8 852**	**100.0%**	**0.81 (0.76, 0.87)**
Total events	2 459		2 818			

Heterogeneity: Ch^2=96.72, df=6 (P<0.0001); I^2=94%

Test for overall effect: Z=6.26 (P<0.00001)

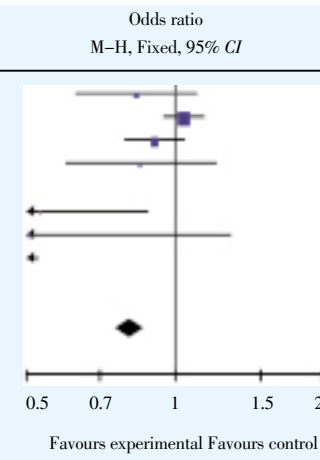

Figure 4. Serious adverse effect of intravenous ZOL on osteoporosis.

Table 2

Subgroup analysis of ZOL on the BMD.

Variables	Trials	Sample size	P value for heterogeneity	BMD		
				OR	95%	*CI*
Age (years)	≤50	2	66/66	0.28	0.67	0.22, 1.11
	>50	6	6 802/6 860	<0.05	3.71	3.02, 4.40
Intervention duration (months)	≤12	4	317/403	0.08	2.56	0.04, 5.16
	>12	7	6 551/6 523	<0.05	3.35	2.77, 3.92

Table 3
Subgroup analysis of ZOL on the fracture.

Variables	Trials	Sample size	*P* value for heterogeneity	BMD		
				OR	95%	*CI*
Age (years)	≤50	1	30/35	–	0.15	0.03, 1.03
	>50	4	8 398/8 364	0.07	0.68	0.59, 0.89
Intervention duration (months)	≤12	1	1 961/1926	–	0.67	0.22, 1.11
	>12	4	6 467/6 473	0.13	0.67	0.54, 0.82

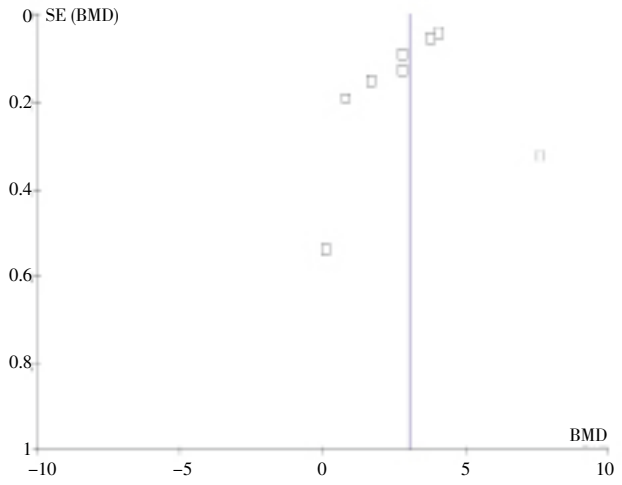

Figure 5. Funnel plot of role of ZOL on BMD.

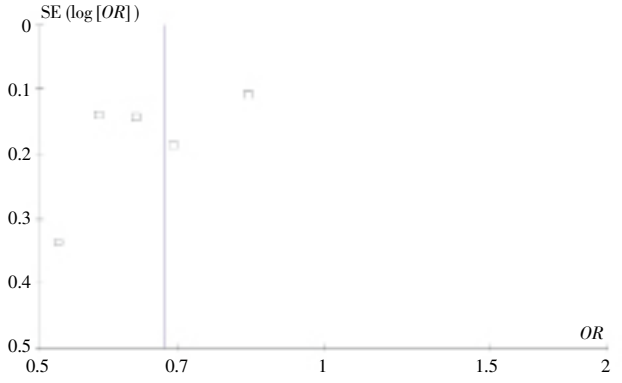

Figure 6. Funnel plot of role of ZOL on fracture.

4. Discussion

This meta-analysis showed that ZOL had better effect on treatment of osteoporosis. These finding provide evidence for the efficacy of ZOL in improving the BMD and reducing the fracture among patients with osteoporosis.

Previously, biosphosphonates are the preferred medications used for osteoporosis treatment and act by inhibiting osteoclastic activity. Previous studies reported that these drugs could greatly reduce the incidence of hip, vertebral and non-vertebral fracture by 50%[18,19]. However, the unsatisfied absorption of intestinal limited the use of these drugs. Intravenous ZOL could be better absorbed and be administered as once-yearly 5-mg intravenous infusion over no less than 15 minutes[20]. Our study pooled 9 studies, and showed a significantly higher BMD of ZOL intervention group than controls, and only one study with small sample showed the ZOL could not increase the BMD[14]. Recently a guideline recommend that the pharmacological therapy be considered for postmenopausal women with osteoporosis and for women without osteoporosis at moderate to high fracture risk, based on a combination of BMD and clinical risk factors[21]. In our study, we found that the ZOL could improve the BMD in individuals, especially increase higher BMD in high risk of osteoporosis, which showed the ZOL could be an effective way in treatment of osteoporosis and has a favorable role in preventing fracture. Furthermore, the heterogeneity between studies showed there might be other factors which influence the effect of ZOL on osteoporosis. After the subgroup analysis regarding the age and intervention duration, the heterogeneity was greatly reduced, but there was still significant heterogeneity between studies. Therefore, some factors such as baseline characteristics of patients, such as BMI, BMD of the baseline, ethnicities, *etc* should be considered.

The safety profile in the ZOL group is better than controls. Lower risk of serious adverse effect was found in ZOL intervention group than the placebo, such as only calcium and vitamine D, or hormone therapy, raloxifene, calcitonin or tibolone along with calcium and vitamin D. The appropriateness and safety of pharmacological therapy in treatment of osteoporosis has been extensively debated[22-25]. Our study provides sufficient evidence for the safety of ZOL by pooling several large sample randomized clinical trials.

There were some limitations in our study. Firstly, there is still great heterogeneity between studies even after subgroup analysis, which indicated further analysis regarding influencing factors should be considered. Secondly, few numbers of studies included in our analysis would limit the statistic power, and therefore, we should performed subgroup analysis regarding the location of BMD or fracture of participants by ZOL intervention.

In conclusion, this present study showed the ZOL could be effective approach in the prevention of osteoporosis, and

could increase the BMD and reduce the risk of facture.

Conflict of interest statement

We declare that we have no conflict of interest.

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