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Original Article

Effects of combined alendronate and alfacalcidol on prevention of fractures in osteoporosis patients: a network meta-analysis

Hong-Bo Shao[1*], Yue-Ming Yao[2*], Zhao-Yan Wang[3], Qing-Fu Zhang[1], Wei Wei[1]

[1]Department of Burn and Plastic Surgery, First Hospital of Hebei Medical University, Shijiazhuang 050031, Hebei, China; [2]Department of Orthopedic, Cardiovascular Diseases Hospital, Shijiazhuang 050037, Hebei, China; [3]Department of Otolaryngology, Second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei, China. [*]Equal contributors.

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Abstract: Background: Published literatures report controversial results about the effect of combined treatment with alendronate and alfacalcidol for the prevention of fractures in osteoporosis patients. Methods: Seven common databases were searched for related randomized controlled trials published up to April, 2015. Bayesian random effects network meta-analysis was used to assess the pairwise odds ratios (OR), 95% credible intervals (CI). Results: Thirteen randomized controlled trials were identified (3710 patients). The network meta-analysis results indicated that combining treatment with alendronate and alfacalcidol was significantly better to prevent bone fractures in osteoporosis patients than alendronate (OR=0.53, 95% CI: 0.19-0.95) and alfacalcidol (OR=0.25, 95% CI: 0.08-0.49). In addition, there was no significant difference for adverse events among the three therapeutic regimen. Conclusions: Combined treatment with alendronate and alfacalcidol was more active than the monotherapies in preventing bone fractures in osteoporosis patients. Large-scale randomized, controlled trials are recommended to confirm the result.

Keywords: Osteoporosis, fractures, alendronate, alfacalcidol, network meta-analysis, drug therapy

Introduction

As the population ages in worldwide, age-related diseases in recent years gradually increase [1]. Osteoporosis, a disease mainly in the elderly, has been growing more common. A recent research showed that up to 49 million individuals had osteoporosis in a number of industrialized countries in North America, Europe, Japan, and Australia [2]. The subsequent fractures caused by osteoporosis not only make patients suffer great physical and mental pain, but also present a serious burden to the family and society [3, 4]. In the European Union, the cost of osteoporosis in 2010 was estimated at 37 billion euro, and costs of treating incident fractures represented 66% of this cost [3].

An effective and safe therapy for osteoporosis remains a priority to prevent the subsequent fractures. In recent years, combined therapies for osteoporosis have been brought to the fore by the approval of Alendronate and vitamin D3 by both the Food and Drug Administration. As inhibiting bone resorption, Alendronate treatment can increase bone mineral density at different skeletal sites and reduce fracture incidence [5, 6]. Alfacalcidol, Dhormone analogs, has been proven to be potent in increasing bone mineral density and reducing fractures in several meta-analysis studies [7-9]. Due to additive effects for bone turnover [10], a combined treatment with Alendronate and alfacalcidol has become a research hotspot. Some preliminary clinical studies showed that the combined treatment was more active than the monotherapies in osteoporosis [11-13]. However, some other researches indicated the combination therapy was no more effective for fracture prevention [14, 15]. Individual studies could not draw solid conclusions, and no meta-analysis exploring the effect of combined treat-

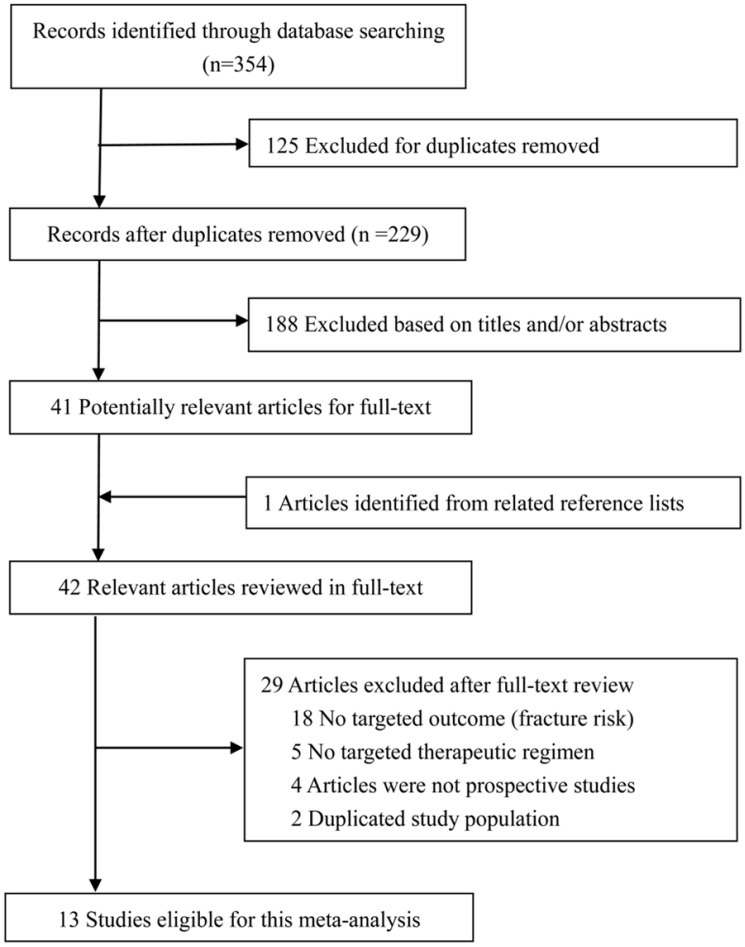

Figure 1. Flow diagram of studies selection in the network meta-analysis.

ment with alendronate and alfacalcidol has been conducted yet. Thus, we performed this network meta-analysis to assess the effect of the combination therapy for the prevention of fractures in osteoporosis patients.

Methods

Search strategy

A systematic literature search, restricted to human studies, was performed using the following databases (PubMed; Web of Science; Scopus; Cochrane Library Clinical Trials; China National Knowledge Infrastructure; China Biology Medical literature database; Database of Chinese Scientific and Technical Periodicals) and the search terms ("alfacalcidol" or "alphacalcidol" or "alendronate") and ("osteoporosis" or "osteoporosis" or "age-related bone loss" or "osteopenia") in various combinations for relevant articles without time restriction (**Figure 1** showed details of the search process and study selection). The last search was performed on April 23, 2015. In addition, we searched and identified studies not captured by our database through reviewing reference lists in retrieved articles.

Inclusion criteria

Each identified study was evaluated against the following predefined criteria:

(1) Population of interest: Osteoporosis patients;

(2) Interventions and Comparators: more than 2 in the following three therapeutic regimen: combined treatment with alendronate and alfacalcidol; alendronate alone; alfacalcidol alone. (A parallel prescription of plain vitamin D and calcium to any specific medications is regarded as a basic therapy or nutritional supplementation and not as a combined treatment of different potent drugs);

(3) Outcomes: Incidence of fractures and corresponding adverse events;

(4) Study Design: Randomized controlled trials. Nonexperimental studies (e.g., cohort, case-control, cross-sectional studies) as well as (systematic) literature reviews, commentaries, and other meta-analyses were excluded;

(5) And studies with more than 15 patients in each arm and more than 10 months of follow-up after the intervention.

Data extraction and quality assessment

A data extraction sheet was developed that included first author, publication year, country where the study was conducted, patient characteristics, study design, interventions, number of participants, incidence of fractures, and adverse events. All data were extracted independently by two reviewers. In cases of dis-

Table 1. Characteristics of randomized controlled trials in the meta-analysis

Author (year)	Country	Type of OP	Therapeutic regimen	Sample size	Age Mean (SD)	Gender M/F	Follow-up Months
Shiraki (1999)	Japan	Primary OP	Alen 5 mg/d	105	63.5 (0.7)	NA	11.2
			Alfa 1 μg/d	105	63.2 (0.6)	NA	
Kushida (2004)	Japan	Postmenopausal OP	Alen 5 mg/d	93	71.2 (5.3)	0/93	36
			Alfa 1 μg/d	86	72.6 (5.7)	0/86	
Ringe (2004)	Germany	Primary OP	Alen 10 mg/d	68	53.3 (11.1)	68/0	36
			Alfa 1 μg/d	66	52.1 (10.9)	66/0	
de Nijs (2006)	Netherlands	Glucocorticoid-Induced OP	Alen 10 mg/d	99	60 (14)	40/59	18
			Alfa 1 μg/d	101	62 (15)	36/65	
Shiraki (2006)	Japan	Primary OP	Alen 5 mg/d	197	70	NA	36
			Alfa 1 μg/d	221	70	NA	
Ones (2007)	Japan	Postmenopausal OP	Alen 10 mg/d + Alfa 0.5 μg/d	46	58.3 (7.2)	0/46	24
			Alen 10 mg/d	44	58.4 (8.7)	0/44	
			Alfa 0.5 μg/d	68	57.9 (6.1)	0/68	
Ringe (2007)	Germany	Primary OP	Alen 10 mg/d + Alfa 1 μg/d	30	65.9 (7.6)	11/19	24
			Alen 10 mg/d	30	65.7 (9.4)	11/19	
			Alfa 1 μg/ d	30	66.4 (9.5)	11/19	
Takata (2007)	Japan	Postmenopausal OP	Alen 10 mg/d	41	65.2 (4.0)	0/41	12
			Alfa 0.5 μg/d	62	66.0 (4.5)	0/62	
Okada (2008)	Japan	Glucocorticoid-Induced OP	Alen 5 mg/d + Alfa 1 μg/d	25	32.5 (1.3)	0/25	18
			Alfa 1 μg/d	22	31.4 (1.8)	0/22	
Takeda (2008)	Japan	Glucocorticoid-induced OP	Alen 5 mg/d	17	49.2 (14.6)	0/17	24
			Alfa 1 μg/d	16	45.0 (13.2)	0/16	
Kitazaki (2009)	Japan	Glucocorticoid-Induced OP	Alen 5 mg/d	16	41.2 (12.8)	10/6	12
			Alfa 1 μg/d	20	38.1 (15.5)	12/8	
Orimo (2011)	Japan	Postmenopausal OP	Alen 5 mg/d + Alfa 1 μg/d	995	76.6 (4.9)	0/995	24
			Alen 5 mg/d	1027	76.6 (4.9)	0/1027	
Ji (2013)	China	Primary OP	Alen 10 mg/d + Alfa 0.5 μg/d	40	67.3 (4.2)	10/30	24
			Alen 10 mg/d	40	65.5 (5.6)	11/29	

OP, osteoporosis; Alen, alendronate; Alfa, alfacalcidol; M, male; F, female; NA, not available.

agreement between the two reviewers, a consensus was achieved through discussion among all of the authors. The Cochrane risk of bias tool was used to assess study quality [16]. This tool assesses five areas of potential bias in randomized controlled trials including randomization, allocation concealment, blinding, reporting of data and other sources of bias.

Statistical analysis

Treatment effects of the different studies were synthesized and indirectly compared by means of a network meta-analysis [17]. The network meta-analysis model was performed within a Bayesian framework, a likelihood distribution, a model with parameters, and prior distributions for these parameters [18]. The comparison of the effects between groups were shown as odds ratio (OR) and its 95% confidence interval (95% CI). The study characteristics varied in different studies, including race, age, gender, drug dose, disease type, follow-up time, etc. So we adopted random effect model rather than fixed effect model. The outputs of the study were in the form of network plot and forest plots. The statistical analysis was performed using software R 3.12 (main packages including gemtc and rjags) and JAGS 3.4.0. [19].

Results

Study characteristics

The procedure of the literature search was presented in **Figure 1**. 13 articles including 3710 osteoporosis patients were finally included in our analysis. General characteristics of the published articles included in this meta-analysis were shown in **Table 1**. Nine trials were conducted in Japan, two in Germany, one in China, and one in Netherlands. Ranges of follow-up periods were from 11.2 to 48 months for these randomized controlled trials. Two trials were

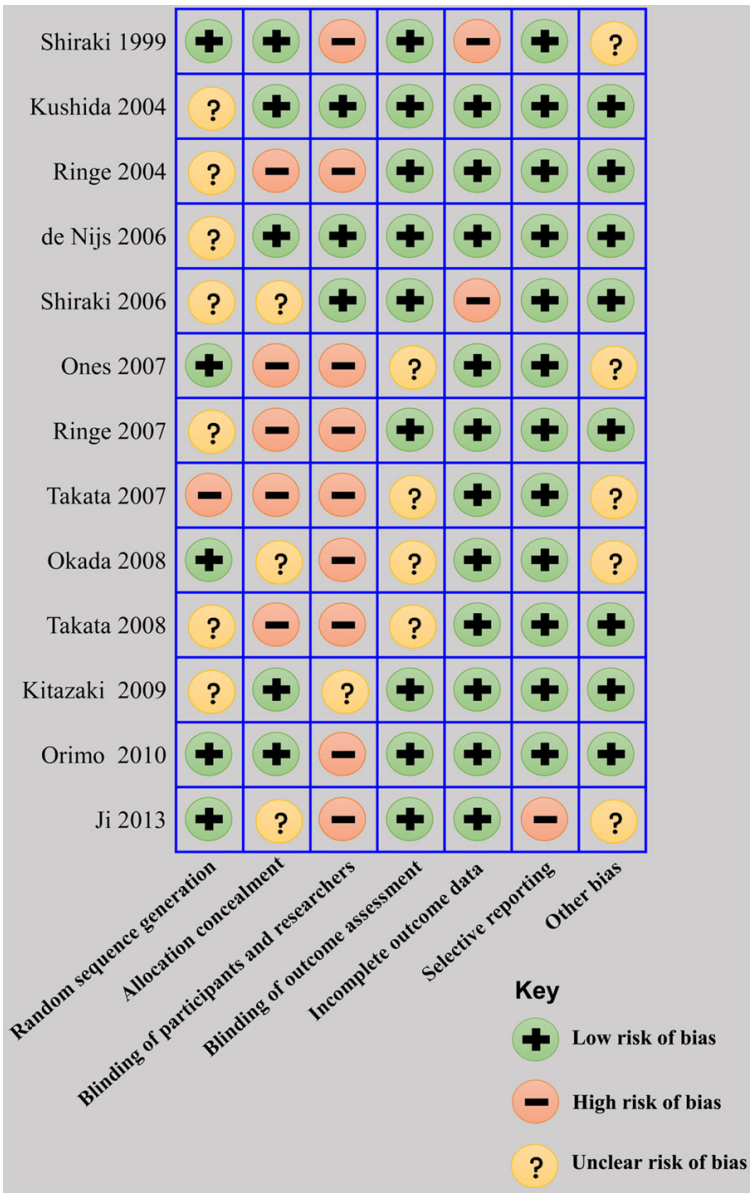

Figure 2. Summary of Cochrane risk of bias for the 13 studies.

designed as three-arm trials namely, three interesting therapeutic regimen were all performed in one trial. The quality of the trials were assessed by the Cochrane Risk of Bias tool (**Figure 2**).

Bone fractures

The network meta-analysis results of bone fractures risk was presented in **Figure 3**. The results indicated that combined treatment with alendronate and alfacalcidol was significantly better to prevent bone fractures in osteoporosis patients than alendronate (OR=0.53, 95% CI: 0.19-0.95) and alfacalcidol (OR=0.25, 95% CI: 0.08-0.49).

Safety

The network meta-analysis results of adverse events showed that there are not significant differences among the three therapeutic regimens (**Figure 4**).

Discussion

Osteoporosis is a common disease characterized by a systemic impairment of bone mass and microarchitecture that results in fragility fractures [20]. Alendronate and alfacalcidol are widely applied in clinical to treat osteoporosis and prevent subsequent fractures [21, 22]. Our study indicated that the combined treatment with alendronate and alfacalcidol was more active than the monotherapies in preventing bone fractures. In addition, no significant difference was detected in adverse events among the three therapeutic regimen. Hence, the combined treatment is better option to treat osteoporosis in clinical.

Bisphosphonates are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases [23]. The bisphosphonates inhibit osteoclastic bone resorption via a mechanism that differs from that of other antiresorptive agents [24, 25]. Similar to all bisphosphonates, alendronate has a high affinity for bone mineral and is taken up during osteoclast resorption. Alendronate inhibits farnesyl pyrophosphate synthetase, one of the enzymes in the mevalonic acid pathway involved in producing isoprenoid compounds that are essential for post-translational modification of small guanosine triphosphate (GTP)-binding proteins, such as Rho, Ras and Rab. Inhibition of this process interferes with osteoclast function and

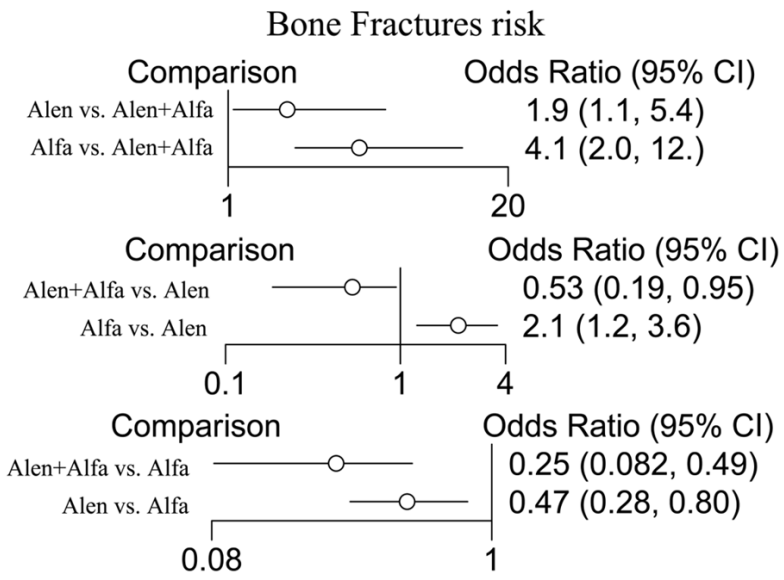

Figure 3. Forest plot of the network meta-analysis for bone fractures risk among osteoporosis patients. Alen, alendronate; Alfa, alfacalcidol; confidence interval.

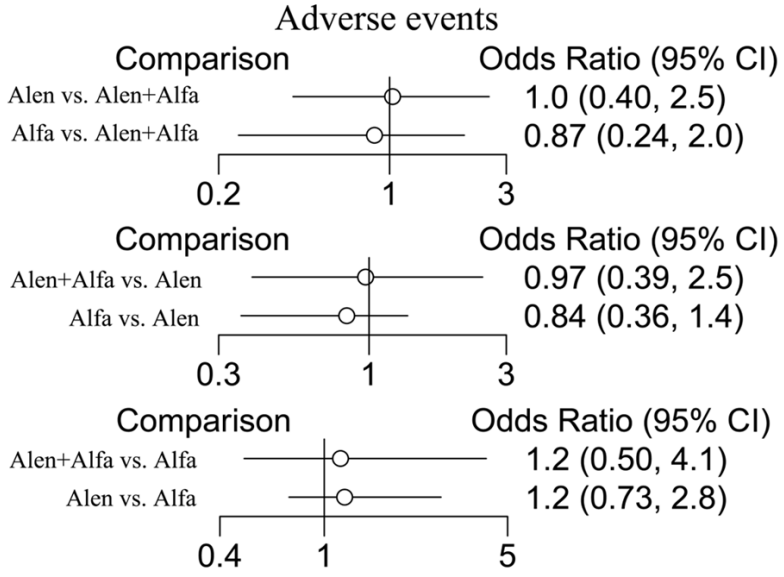

Figure 4. Forest plot of the network meta-analysis for adverse events among osteoporosis patients. Alen, alendronate; Alfa, alfacalcidol; confidence interval.

survival. Finally alendronate specifically inhibits bone resorption [26, 27].

Alfacalcidol is an active metabolite of Vitamin D, which performs important functions in regulation of the calcium balance and the bone metabolism. Alfacalcidol is Vitamin D-hormone analog which is activated by the enzyme 25-hydroxylase in the liver for systemic and in osteoblasts for local D-hormone actions. The active form of vitamin D3 binds to intracellular receptors that then increases the serum calcium concentrations by: increasing gastrointestinal absorption of phosphorus and calcium, increasing osteoclastic resorption, and increasing distal renal tubular reabsorption of calcium [28, 29].

The superior efficacy of the combined treatments of alendronate and alfacalcidol may be based on different modes of action complementing each other: increased inhibition of bone resorption by different pathways [26, 30, 31], enhanced bone formation [32], improvement of trabecular microstructure and increase of "bone quality" muscles [33].

This network meta-analysis firstly used direct and indirect evidence to estimate the effect of combined treatments in osteoporosis patients. However, the potential limitations of this meta-analysis should be considered. First, because of our topic on all kinds of osteoporosis, the application of the current outcomes should take into consideration the specific characteristics of different type osteoporosis. Second, because of the inability to obtain raw data, we could perform only a study-level but not a patient-level meta-analysis, which would have enabled us to control some confounders, such as gender, age, follow-up time, and so on. Third, although significant better effect of combined treatments than the monotherapies was found, the recurring result should be confirmed in future, for a few samples included.

Conclusion

This network meta-analysis suggested that combining treatment with alendronate and alfacalcidol was better than the monotherapies in preventing bone fractures in osteoporosis patients. Large-scale randomized, controlled trials are recommended to confirm the result.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hong-Bo Shao, Department of Burn and Plastic Surgery, First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang 050031, Hebei, PR China. Tel: +86-31185917102; E-mail: yyming7209y@sohu.com

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