Systematic Review and Meta-Analysis

Medicine®

OPEN

Meta-regression analysis of the efficacy of alendronate for prevention of glucocorticoid-induced fractures

Mei Qiu, MS[a,*], Liangliang Ding, MS[b], Miao Zhang, BS[c], Jinhao Lin, MS[d], Hua Huang, BS[e], Kaikai Li, BS[f]

Abstract

Background: What affects the efficacy of alendronate for prevention of glucocorticoid-induced (GI) fractures remains unclear. We aimed to explore the factors affecting alendronate's efficacy, and further identify subgroup effects of alendronate in preventing GI fractures.

Methods: We searched 3 databases. Random-effects meta-analysis was conducted to synthesize risk ratio (RR) and 95% confidence interval (CI) for each endpoint. Meta-regression analysis was used to explore sources of heterogeneity, and subgroup analysis was used to address heterogeneity and evaluate subgroup effects. We detected publication bias using funnel plots and Egger tests.

Results: We included 13 papers from 12 unique studies involving 46431 participants. Glucocorticoid (GC) dosage ($P = .053$) and proportion of previous vertebral fracture (PVF) ($P = .047$) were probably 2 sources of heterogeneity in meta-analysis for vertebral fractures, while GC duration ($P = .020$) was probably 1 for nonvertebral fractures. Alendronate reduced vertebral fractures in the high dosage subgroup (RR 0.61, 95% CI 0.44–0.86), but didn't in the low dosage subgroup (RR 1.56, 95% CI 0.20–12.02). Alendronate reduced vertebral fractures (RR 0.53, 95% CI 0.40–0.68) in the subgroup of PVF proportion <5%, but didn't (RR 0.76, 95% CI 0.42–1.37) in the subgroup of this proportion ≥5%. Alendronate reduced nonvertebral and hip fractures, whether in primary or in secondary prevention subgroup.

Conclusions: The findings in our study support that alendronate is used for the primary and secondary prevention of GI fractures, but do not support that alendronate is recommended as a first-line agent for patients receiving a low dose of GCs or patients with PVF.

Abbreviations: BMD = bone mineral density, CI = confidence interval, GCs = glucocorticoids, GI = glucocorticoid-induced, GIOP = glucocorticoid-induced osteoporosis, RCT = randomized controlled trial, RR = risk ratio.

Keywords: alendronate, glucocorticoid-induced fractures, glucocorticoids, osteoporosis, secondary osteoporosis

1. Introduction

Glucocorticoids (GCs) are widely used for the treatment of inflammatory conditions and autoimmune diseases. GC use, however, may lead to various side effects and serious adverse events. Glucocorticoid-induced osteoporosis (GIOP), as one of GCs' side effects, is the most common secondary osteoporosis[1] and osteoporotic fractures are the most common serious adverse events which occur in patients receiving long-term or high doses of GCs.[2–4] Therefore, it is important for susceptible individuals to use anti-osteoporosis agents for the prevention of glucocorticoid-induced (GI) fractures.

Although alendronate and other oral bisphosphonates are recommended as first-line agents for primary osteoporosis[5] and GIOP,[6] it isn't suggestive that oral alendronate is suitable for any patient with GIOP. Clinicians and patients need to know what probably affects the efficacy of alendronate in patients receiving long-term GCs and some specific conditions in which alendronate is not able to reduce GI fractures. Several meta-analyses[7–11] were conducted to aim to assess the effectiveness of alendronate in patient with GIOP. However, all of these studies failed to explore the factors affecting alendronate's efficacy and failed to find out specific patients for whom alendronate was not suitable. Besides, none of them included 3 large-scale cohort studies[12–14] newly published to provide the newest evidence about alendronate for GIOP.

Editor: Fateh Rahimi.

ORCiD numbers: Mei Qiu (0000-0001-5013-657X).

The authors have no funding and conflicts of interest to disclose. Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files.

[a] Department of General Medicine, Shenzhen Longhua District Central Hospital, Shenzhen, [b] Department of Endocrinology, First Affiliated Hospital of Yangtze University, Jingzhou, [c] Department of Nephrology, [d] Department of Gastroenterology, Shenzhen Hospital of Beijing University of Chinese Medicine, Shenzhen, [e] Department of Neurology, Hankou Hospital of Wuhan City, Wuhan, [f] Department of General Medicine, The Central Hospital of Tuoshi Town, Tianmen, China.

[*] Correspondence: Mei Qiu, Department of General Medicine, Shenzhen Longhua District Central Hospital, Shenzhen 518110, China (e-mail: 13798214835@sina.cn).

How to cite this article: Qiu M, Ding L, Zhang M, Lin J, Huang H, Li K. Meta-regression analysis of the efficacy of alendronate for prevention of glucocorticoid-induced fractures. Medicine 2020;99:42(e22690).

Received: 14 February 2020 / Received in final form: 23 June 2020 / Accepted: 6 September 2020

http://dx.doi.org/10.1097/MD.0000000000022690

Thus, we performed this meta-analysis to aim to explore what affects the efficacy of alendronate for prevention of GI fractures, and find out subgroup effects of alendronate using vertebral, nonvertebral, and hip fractures as primary outcomes in order to provide specific evidence about alendronate used for GIOP.

2. Methods

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[15] The protocol for this study has been registered in the Research Registry (www.researchregistry.com; registration number: reviewregistry775).

2.1. Study inclusion and exclusion criteria

The endpoints of interest were primary endpoints including vertebral fractures, nonvertebral fractures and hip fractures, and secondary endpoints including adverse events, serious adverse events and tolerability (withdrawals due to adverse events).

This meta-analysis included studies which were:

(1) randomized controlled trials (RCTs) or cohort studies with a follow-up period of at least 12 months;
(2) studies that enrolled patients beginning or continuing long-term (≥3 months)[6] GCs with a low dosage (<7.5 mg/day) or high dosage (≥7.5 mg/day)[6] of prednisone or equivalent;
(3) studies in which active treatment was oral alendronate, and comparator treatment was placebo, no alendronate use, vitamin D, calcitriol or alfacalcidol; and
(4) studies which measured 1 or more than 1 primary endpoint.

Articles were excluded when:

(1) identical data were re-analyzed;
(2) participants received inhaled GCs;
(3) participants were children and adolescents; or
(4) the daily dosage of alendronate use was 2.5 mg.

Patients beginning long-term GCs are those starting alendronate within 3 months of initiating GCs (ie, those in the primary prevention subgroup), while patients continuing long-term GCs are those starting alendronate beyond 3 months of initiating GCs (ie, those in the secondary prevention subgroup).[7]

2.2. Information sources and search strategy

Three literature databases (PubMed, Embase, and Cochrane Library) were systematically searched for English-language articles published from the date of database inception to January 8, 2019, without sample size restrictions. To find out all relevant studies, we used the multifarious search strategies, such as, "Bone and Bones/drug effects [MeSH Terms]", "corticosteroid* [Text Word] OR steroid* [Text Word] OR glucocorticoid* [Text Word]", and "Alendronate [MeSH Terms] OR Alendronate [Text Word]". The full search strategies are listed in Table S1, http://links.lww.com/MD/F8 (Supplemental Content 1, which shows the search strategies). In addition, those references in previous systematic reviews or meta-analyses in the same field were assessed for eligibility and Google Scholar was also searched to include relevant primary studies.

2.3. Study selection

Two authors independently excluded duplicated records at first, and then excluded irrelevant ones by reviewing the titles and abstracts of remaining records, and finally used the full-text version to assess final eligibility when 2 or 1 of them considered a paper as potentially eligible. Discussion between them or the involvement of a third author would address possible disagreements.

2.4. Data extraction and risk of bias assessment

From each eligible paper 2 authors independently extracted name of first author, publication year, study design (double-blind RCT, not double-blind RCT, or cohort study), recruiting area, follow-up duration, mean age, proportion of women, proportion of Caucasians, dose of adjuvant therapy (calcium or vitamin D), dose of alendronate, type of comparator treatment, sample size of each group, GC duration (the duration of glucocorticoid use prior to study enrollment), GC dosage (the daily dosage of prednisone or equivalent during the study), proportion of previous vertebral fracture, proportion of previous anti-osteoporotic therapy, proportion of baseline immunosuppressant use, lumbar spine bone mineral density (BMD) T score at baseline, total hip BMD T score at baseline, 10-year probability of major osteoporotic fracture computed via the Fracture Risk Assessment Tool ,[16] and outcome data.

Included RCTs were assessed for quality by 2 independent authors based on the Jadad scale of which the final score is an integer of less than or equal to 5,[17] while included cohort studies were assessed for quality based on the Newcastle-Ottawa Scale (NOS) of which the final score is an integer of less than or equal to 9.[18] Discussion between them or the involvement of a third author would address possible disagreements on data extraction or quality assessment.

2.5. Statistical analysis

Meta-analysis was performed for each endpoint to calculate pooled risk ratio (RR) and 95% confidence interval (CI) of RR. To provide a conservative estimate of effect, we performed meta-analysis using the random-effects model instead of the fixed-effects model.[7,19] 95% CI not including 1.0 or $P < .05$ is taken for statistical significance. We evaluated between-study heterogeneity using Cochran Q test and quantified it using I^2. $I^2 > 50\%$ or P from Cochran Q test < 0.1 is considered as substantial heterogeneity.[7,20] We performed meta-regression analysis to explore sources of heterogeneity for primary outcomes when I^2 wasn't equal to 0 and for secondary outcomes when substantial heterogeneity was found in meta-analysis. P from meta-regression analysis <.1 denotes possible sources of heterogeneity, and then according covariates would be used for subgroup analysis to address heterogeneity. Publication bias was detected by funnel plots and Egger tests.[21] The covariates used for meta-regression analysis were follow-up duration (months), mean age (years), proportion of women (%), GC dosage (mg/d), spine BMD, hip BMD, proportion of previous vertebral fracture (%), and GC duration (≥3 months or <3 months). All statistical analyses were done using Stata software, version 15.1 (StataCorp LLC, College Station, TX).

2.6. Ethical statement

The data analyzed in this study were extracted from previously published studies, and therefore ethical approval was not necessary.

Table 1

Characteristics and quality assessment of included studies.

Paper id	Study	Recruiting area	Double-blind	Follow-up (mo)	Jadad score	Part 1	Part 2	Part 3	Adjuvant therapy		Sample size	
									Calcium (mg/d)	Vitamin D (IU/d)	Group 1	Group 2
1[22]	de Nijs 2006	The outpatient clinics of 23 departments of rheumatology in the Netherlands	Yes	18	5	2	2	1	500	400	98	100
2[23]	Lems 2006	Netherlands, Belgium	No	12	2	1	1	0	500 or 1000	400	94	69
3[24]	Saag 1998	15 centers in the United States and 22 centers in 15 other countries	Yes	12	5	2	2	1	800–1000	250–500	318	159
4[25]	Adachi 2001	15 centers in the United States and 22 centers in 15 other countries	Yes	24	5	2	2	1	800–1000	250–500	147	61
5[26]	Stoch 2009	USA	Yes	12	5	2	2	1	1000	400	114	59
6[27]	Tee 2012	Singapore	Yes	12	5	2	2	1	360	400	22	22
7[12]	Axelsson 2017	Sweden	Cohort study	15.8	9*	–	–	–	87.5%	87.5%	1802	1802
8[13]	Bergman 2018	Sweden	Cohort study	14.5	8*	–	–	–	78.3%	78.3%	16890	16890
9[14]	Amiche 2018	Canada	Cohort study	12	8*	–	–	–	NR	NR	3945	3945
10[28]	Shane 2004	390 at the Columbia-Presbyterian Medical Center and 42 at the Newark-Beth Israel Medical Center	Yes	12	5	2	2	1	945	1000	74	75
11[29]	Tanaka 2015	Japan	No	12	2	1	0	1	NR	NR	33	28
12[30]	Sambrook 2003	4 Australian centers	No	24	3	2	0	1	600	–	64	64
13[31]	Okada 2008	Japan	No	18	2	1	0	1	600	Alfacalcidol, 1 μg/day	17	16

Double-blind: is it a double-blind randomized controlled trial (RCT)?.

Part 1, the score of randomization; Part 2, the score of double blinding; Part 3, the score of withdrawals and dropouts.

d = day, mo = months, NR = No report.

* Cohort studies were assessed for quality by the Newcastle-Ottawa Scale (NOS).

Adjuvant therapy: all patients from different groups of studies took the identical dosage of calcium and/or vitamin D daily for the duration of the study as adjuvant therapy.

3. Results

3.1. Characteristics of included studies

The flowchart of study selection is shown in Fig. S1, http://links.lww.com/MD/F9 (Supplemental Content 2, which shows the process of study selection), we found out 1509 records at first, of which 13 papers[12–14,22–31] from 12 unique studies involving 46431 participants met the inclusion criteria and were used for quantitative synthesis. Table 1 shows study characteristics and the results of quality assessment. Among 12 unique studies, 3[12–14] were cohort studies, the others were RCTs. Included RCTs had an average Jadad score of 3.8 while included observational studies had a NOS score of 8 or 9. All studies except 2[14,29] involved the application of adjuvant therapy (namely, supplemental calcium or vitamin D).

Table S2, http://links.lww.com/MD/F10 (Supplemental Content 3, which presents the baseline data in included studies) shows the baseline data in included studies. Mean age, in the range of 32 to 80 years, had an average value of 59.1 years. In 6 of the included studies GC duration was less than 3 months, and in 2 of them GC dosage was less than 7.5 mg/d. Proportion of previous vertebral fracture, in the range of 0 to 47.6%, had an average value of 9.5% and 2 missing values. In addition, all outcome data in included studies are provided in Table S3, http://links.lww.com/MD/F11 (Supplemental Content 4, which provides the outcome data in included studies).

3.2. Meta-analyses

Compared with comparator treatment, alendronate showed a significant reduction in vertebral fractures (RR 0.65, 95% CI 0.45–0.95, I^2 41.8%), nonvertebral fractures (RR 0.67, 95% CI 0.54–0.82, I^2 48.3%) and hip fractures (RR 0.53, 95% CI 0.37–0.74, I^2 48.7%). No significant difference between 2 groups was observed in adverse events (RR 0.99, 95% CI 0.92–1.06, I^2 3.5%), serious adverse events (RR 0.81, 95% CI 0.51–1.27, I^2 29.3%) and tolerability (RR 0.62, 95% CI 0.38–1.01, I^2 0%). The detailed meta-analysis results are shown in Figure S2A-S2F, http://links.lww.com/MD/F12 (Supplemental Content 5, which presents the forest plots from meta-analyses). Those I^2 values suggested that it was essential to perform meta-regression analysis to explore sources of heterogeneity for primary endpoints since I^2 wasn't equal to 0 for any primary endpoint, while it wasn't essential for secondary endpoints due to the absence of substantial heterogeneity for any secondary endpoint.

3.3. Meta-regression analyses

Table 2 presents the results of meta-regression analysis for 3 primary outcomes with 8 different covariates respectively used. According to the criterion of P less than .1, GC dosage ($P = .053$) and proportion of previous vertebral fracture ($P = .047$) were probably 2 sources of heterogeneity in meta-analysis for vertebral fractures, while duration of GC use ($P = .020$) was probably 1 for nonvertebral fractures. Meanwhile, based on their regression

Table 2

Meta-regression analysis for primary outcomes using different covariates.

Outcome	Covariate	Number of study	Regression coefficient	Standard error of regression coefficient	*P* value
Vertebral fractures	a	10	−0.126	0.075	.134
Vertebral fractures	b	10	0.021	0.021	.351
Vertebral fractures	c	10	−0.025	0.013	.103
Vertebral fractures	d	10	**−0.044**	0.019	**.053**
Vertebral fractures	e	4	3.205	3.263	.429
Vertebral fractures	f	3	−0.654	2.389	.830
Vertebral fractures	g	8	**0.040**	0.016	**.047**
Vertebral fractures	h	10	0.172	0.514	.747
Nonvertebral fractures	a	7	−0.002	0.045	.972
Nonvertebral fractures	b	7	−0.008	0.017	.654
Nonvertebral fractures	c	7	−0.002	0.013	.889
Nonvertebral fractures	d	7	−0.002	0.020	.907
Nonvertebral fractures	e	4	0.539	1.247	.708
Nonvertebral fractures	f	3	0.731	1.232	.659
Nonvertebral fractures	g	6	0.004	0.019	.864
Nonvertebral fractures	h	7	**−0.362**	0. 108	**.020**
Hip fractures	a	4	−0.073	0.139	.651
Hip fractures	b	4	−0.067	0.030	.153
Hip fractures	c	4	−0.017	0.044	.741
Hip fractures	d	4	0.023	0.030	.522
Hip fractures	e	1	–	–	–
Hip fractures	f	1	–	–	–
Hip fractures	g	4	−0.003	0.073	.975
Hip fractures	h	4	−0.444	0.205	.163

a, follow-up duration (months); b, mean age (years); c, proportion of women (%); d, GC dosage (mg/d); e, lumbar spine bone mineral density T score at baseline; f, total hip bone mineral density T score at baseline; g, proportion of previous vertebral fracture (%); h, duration of GC use (binary variable; 1 denotes "≥3 months", and 0 denotes "<3 months").

coefficients, the RR of alendronate versus comparator treatment in preventing vertebral fractures probably decreased by 4.3% for 1 mg increase in daily GC dosage, and increased by 4.1% for 1% increase in proportion of previous vertebral fracture; and the RR of alendronate in preventing nonvertebral fractures in the secondary prevention subgroup probably decreased by 30.4% compared with that in the primary prevention subgroup. No other findings with *P* less than .1 were observed via meta-regression analysis.

3.4. Subgroup analyses

Fig. 1 shows the results of subgroup meta-analysis stratified by GC dosage for vertebral fractures. Substantial heterogeneity was found in overall meta-analysis ($I^2 = 41.8\%$, $P = .079$), and wasn't found in both subgroup meta-analyses ($I^2 = 35.5\%$ or 37.9%, $P = .146$ or .204); which validated that GC dosage was 1 source of heterogeneity for vertebral fractures. Meanwhile, compared with comparator treatment, alendronate reduced vertebral fracture risk in the subgroup of GC dosage ≥7.5 mg/d (RR 0.61, 95% CI 0.44–0.86), and didn't in the subgroup of GC dosage <7.5 mg/d (RR 1.56, 95% CI 0.20–12.02).

Figure 2 shows the results of subgroup meta-analysis stratified by proportion of previous vertebral fracture for vertebral fractures. Compared with comparator treatment, alendronate reduced vertebral fracture risk in the subgroup of proportion of previous vertebral fracture <5% (RR 0.53, 95% CI 0.40–0.68, I^2 0%), and didn't in the subgroup of proportion of previous vertebral fracture ≥5% (RR 0.76, 95% CI 0.42–1.37, I^2 50.7%). Given substantial heterogeneity found in the latter subgroup, we performed sensitivity analysis in this subgroup by excluding Lems et al study,[23] and the results (Fig. 3) showed that alendronate didn't also reduce vertebral fracture risk (RR 0.67, 95% CI 0.41–1.11) with substantial heterogeneity eliminated ($I^2 = 35.4\%$).

Figure 4 shows the results of subgroup meta-analysis stratified by GC duration for nonvertebral fractures. Heterogeneity was completely eliminated by this subgroup analysis, and alendronate reduced nonvertebral fracture risk both in the secondary prevention subgroup (RR 0.58, 95% CI 0.50–0.68, I^2 0%) and in the primary prevention subgroup (RR 0.83, 95% CI 0.72–0.96, I^2 0%). GC duration was probably 1 source of heterogeneity for hip fractures since GC duration was 1 source of heterogeneity for nonvertebral fractures which contained hip fractures. Accordingly, we performed subgroup analysis stratified by GC duration for hip fractures, and the results (Fig. 5) showed alendronate reduced hip fracture risk both in the secondary prevention subgroup (RR 0.43, 95% CI 0.30–0.60, I^2 0%) and in the primary prevention subgroup (RR 0.66, 95% CI 0.53–0.82, I^2 0%).

3.5. Publication bias assessment

The results (Fig. S3A-S3F, http://links.lww.com/MD/F13, Supplemental Content 6, which shows the funnel plots and *P* values from Egger tests) of funnel plots and Egger tests weren't suggestive of publication bias in meta-analysis for any outcome.

4. Discussion

4.1. Main findings and comparison with previous studies

We carried out a systematic review and meta-analysis to have assessed the anti-fracture efficacy and safety of alendronate in preventing GI fractures, to have explored what affects the efficacy

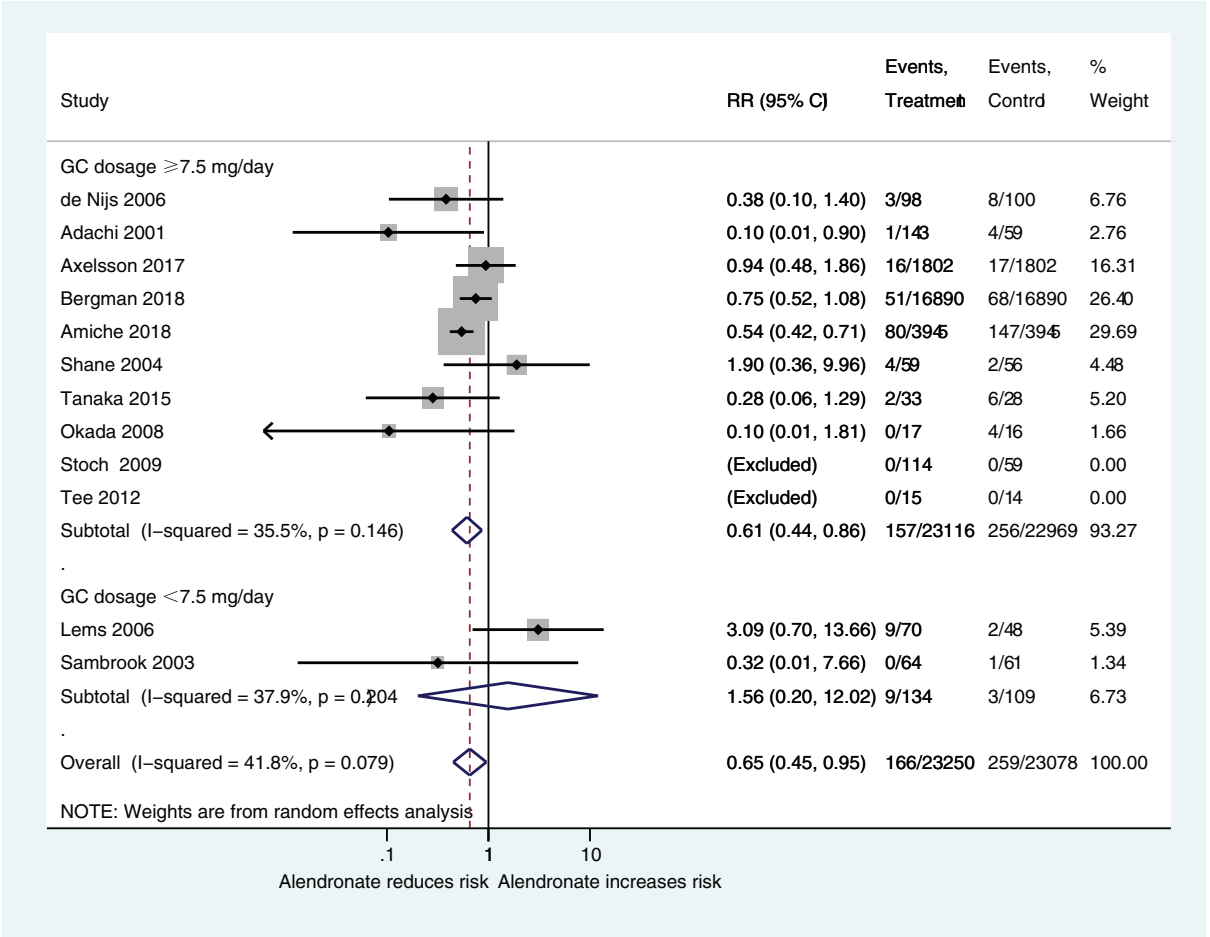

Figure 1. Subgroup meta-analysis stratified by GC dosage for vertebral fractures.

of alendronate, and to have identified subgroup effects of alendronate. Accordingly, this study has produced 3 key findings as follows.

First, our meta-analysis is the first 1 which found the subgroup effect of alendronate based on GC dosage. Alendronate reduced the risk of vertebral fractures in the high dosage subgroup (RR 0.61, 95% CI 0.44–0.86), but didn't in the low dosage subgroup (RR 1.56, 95% CI 0.20–12.02). The finding is supported by the result found in this study that the RR of alendronate versus comparator treatment in reducing vertebral fractures possibly decreased by 4.3% for 1 mg increase in daily GC dosage, and by the fact confirmed in 2 other studies[27,32] that alendronate had greater promotion effect on BMD as GC dosage increased. Thus, our study supports alendronate is used for prevention of vertebral fractures in patients receiving a high dosage of GCs, but doesn't support alendronate is used in patients receiving a low dosage of GCs although a prednisolone dose of 2.5 to 7.5 mg/d also leads to an increase in fracture risk.[6]

Second, our meta-analysis is the first 1 which found the subgroup effect of alendronate based on proportion of previous vertebral fracture. Alendronate reduced vertebral fracture risk (RR 0.53, 95% CI 0.40–0.68, I^2 0%) in the subgroup of this proportion <5%, but didn't (RR 0.76, 95% CI 0.42–1.37, I^2 50.7%) in the subgroup of this proportion ≥5%, in which alendronate didn't also reduce this risk (RR 0.67, 95% CI 0.41–1.11, I^2 35.4%) even when substantial heterogeneity was eliminated by sensitivity analysis. The finding is supported by the result of meta-regression analysis in this study that the RR of alendronate versus comparator treatment in reducing vertebral fractures probably increased by 4.1% for 1% increase in this proportion. Similarly, several RCTs[33–37] demonstrated that bisphosphonates (eg, alendronate and risedronate) were less efficacious than non-bisphosphonate agents (eg, teriparatide and romosozumab) in preventing osteoporotic fractures among the population with severe osteoporosis or a higher proportion of prevalent vertebral fracture. Thus, the finding is probably suggestive that alendronate is suitable for prevention of GI vertebral fractures in patients without prevalent vertebral fracture, but isn't in patients with prevalent vertebral fracture.

Third, our meta-analysis is also the first 1 which confirmed the anti-fracture efficacy of alendronate for both the primary prevention and the secondary prevention of GIOP. Alendronate reduced nonvertebral fracture risk (RR 0.83, 95% CI 0.72–0.96, I^2 0%) and hip fracture risk (RR 0.66, 95% CI 0.53–0.82, I^2 0%) in the primary prevention subgroup, and reduced nonvertebral fracture risk (RR 0.58, 95% CI 0.50–0.68, I^2 0%) and hip fracture risk (RR 0.43, 95% CI 0.30–0.60, I^2 0%) in the secondary prevention subgroup. Similarly, a Cochrane review[38] confirmed the anti-fracture efficacy of alendronate for the primary and secondary prevention of postmenopausal osteopo-

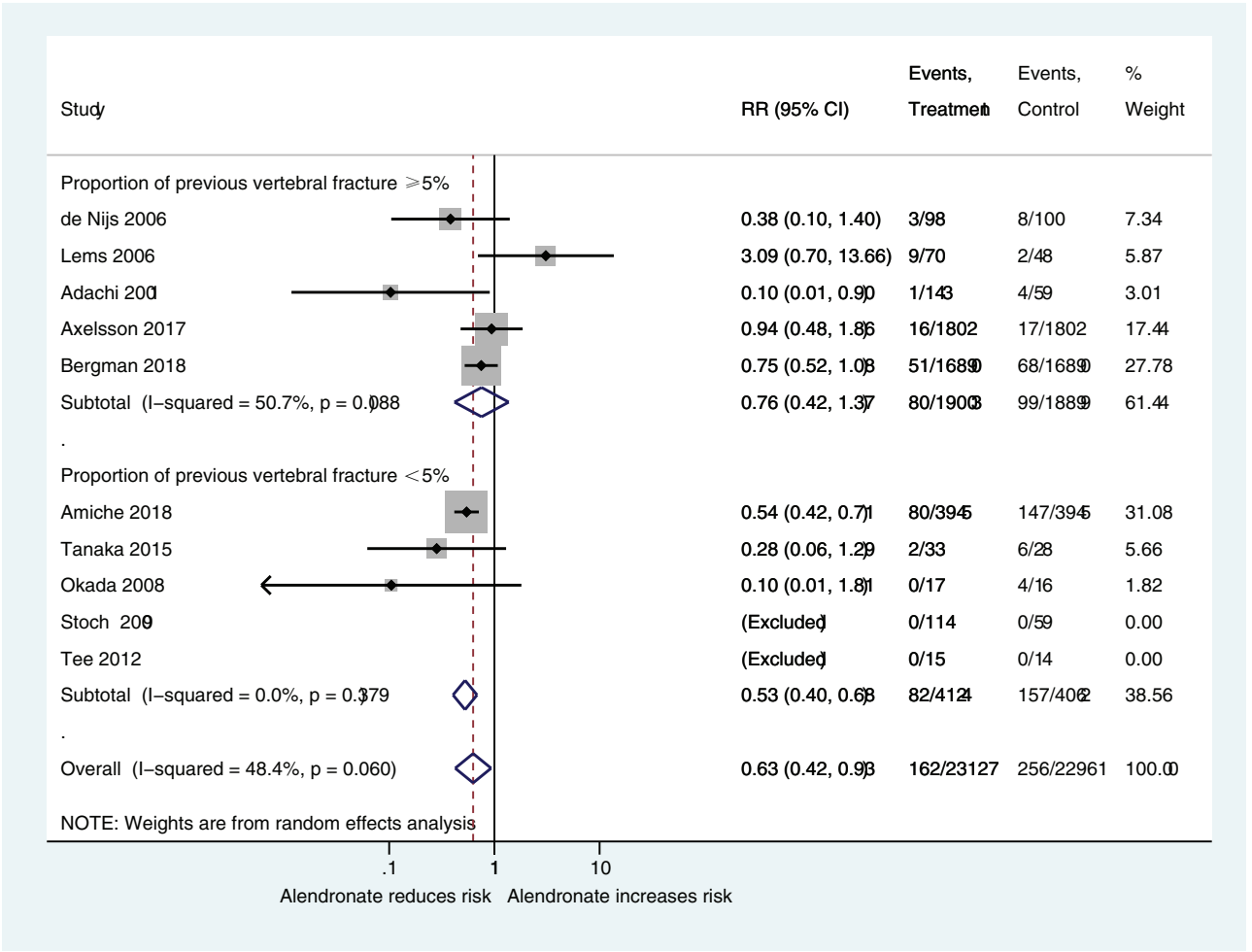

Figure 2. Subgroup meta-analysis stratified by proportion of previous vertebral fracture for vertebral fractures.

rosis, 1 other Cochrane review[7] confirmed the anti-fracture efficacy of oral bisphosphonates as a whole in patients with GIOP, and 2 other meta-analyses[10,11] confirmed the effectiveness of alendronate in increasing BMD in patients with GIOP. Consistent with the finding about the safety and tolerability of alendronate in this study, the 4 meta-analyses[7,10,11,38] also demonstrated alendronate had the same safety and tolerability as control treatment.

4.2. Strengths, limitations, and implications for future studies

This study is the first 1 which explored what affected the efficacy of alendronate for prevention of GI fractures via meta-regression analyses, and which assessed the different subgroup effects of alendronate via appropriate subgroup meta-analyses in which heterogeneity was reduced or completely eliminated. Meanwhile, included studies generally had higher quality according to the quality score, and there was no publication bias found in meta-analysis for any endpoint. On the contrary, this study has several limitations as follows.

First, we performed univariate meta-regression analysis and subgroup analysis based on study-level data due to the limited number of included studies and the absence of individual patient data. Therefore, those relationships and subgroup effects found in the study should be confirmed via analysis of individual patient data.

Second, we failed to conduct more specific subgroup analyses by simultaneously using GC dosage and GC duration to stratify due to the limited data available. Therefore, further studies are needed to provide medical evidence for more specific patients by performing more specific subgroup analyses.

Third, although our findings have some generalizability since included studies had various baseline data (eg, mean age varied from 32 to 80 years, proportion of women varied from18.1% to 100%, and proportion of Caucasians varied from 0% to 90%), proportion of previous anti-osteoporotic therapy in all included studies was 0% except 2 which didn't report this proportion. Thus, the anti-fracture efficacy of alendronate this study revealed should be evaluated again in patients having previously received osteoporosis drugs.

Fourth, since patients in both alendronate group and control group in most of included studies received supplemental calcium and vitamin D, the efficacy this study evaluated, strictly speaking, was produced by the combination of alendronate and supplements of calcium and vitamin D. Therefore, further studies are required to explore whether there is an interaction effect between alendronate and supplements given that calcium and vitamin D

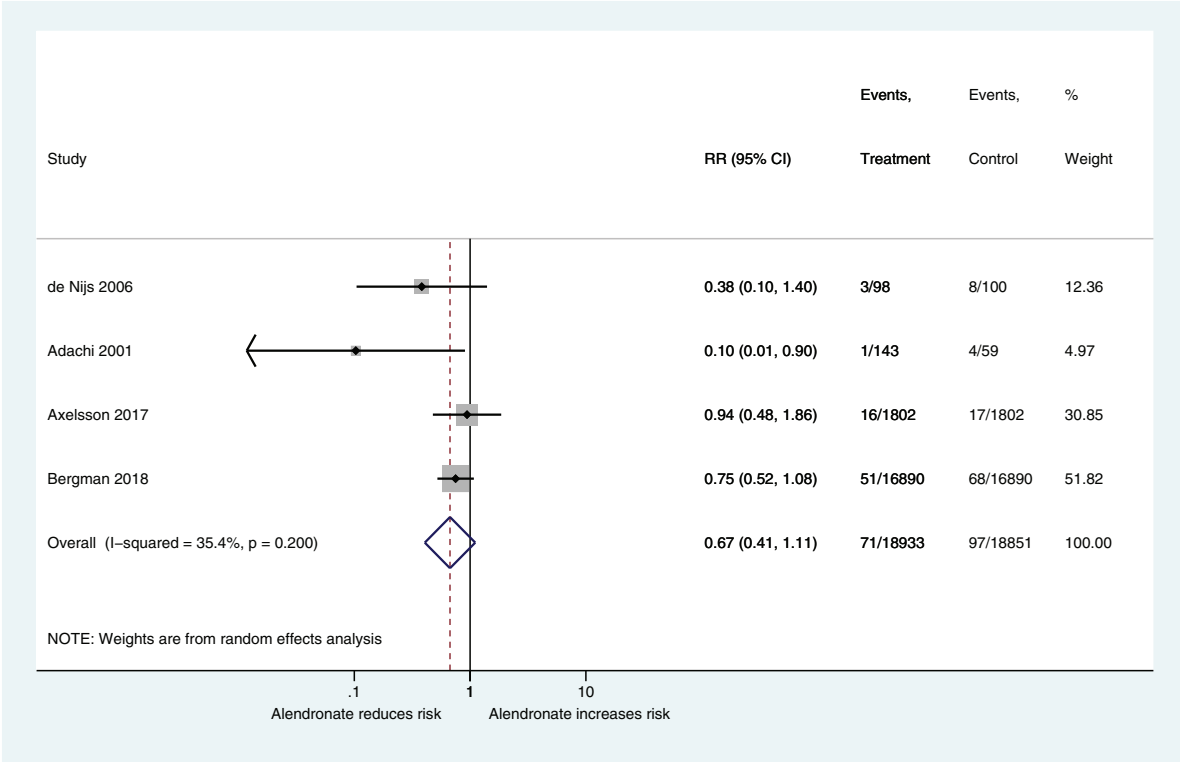

Figure 3. Sensitivity meta-analysis for vertebral fractures in the subgroup of proportion of previous vertebral fracture ≥5%.

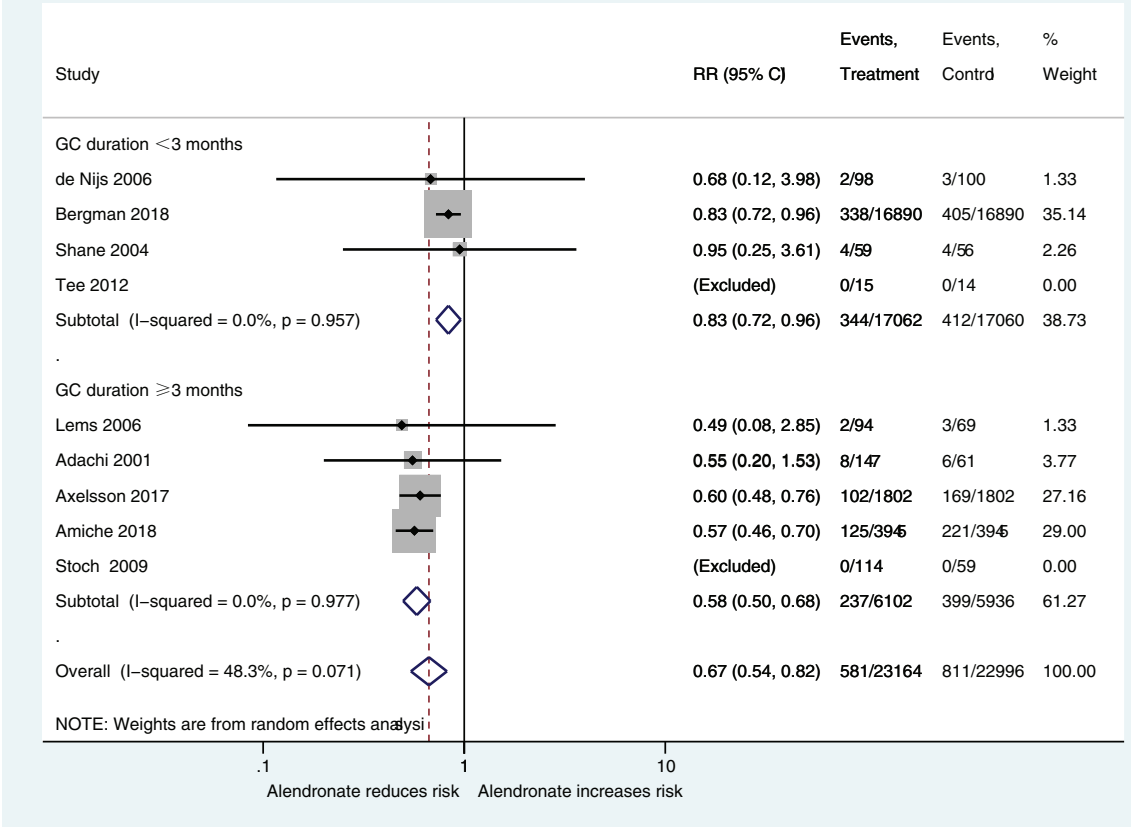

Figure 4. Subgroup meta-analysis stratified by GC duration for nonvertebral fractures.

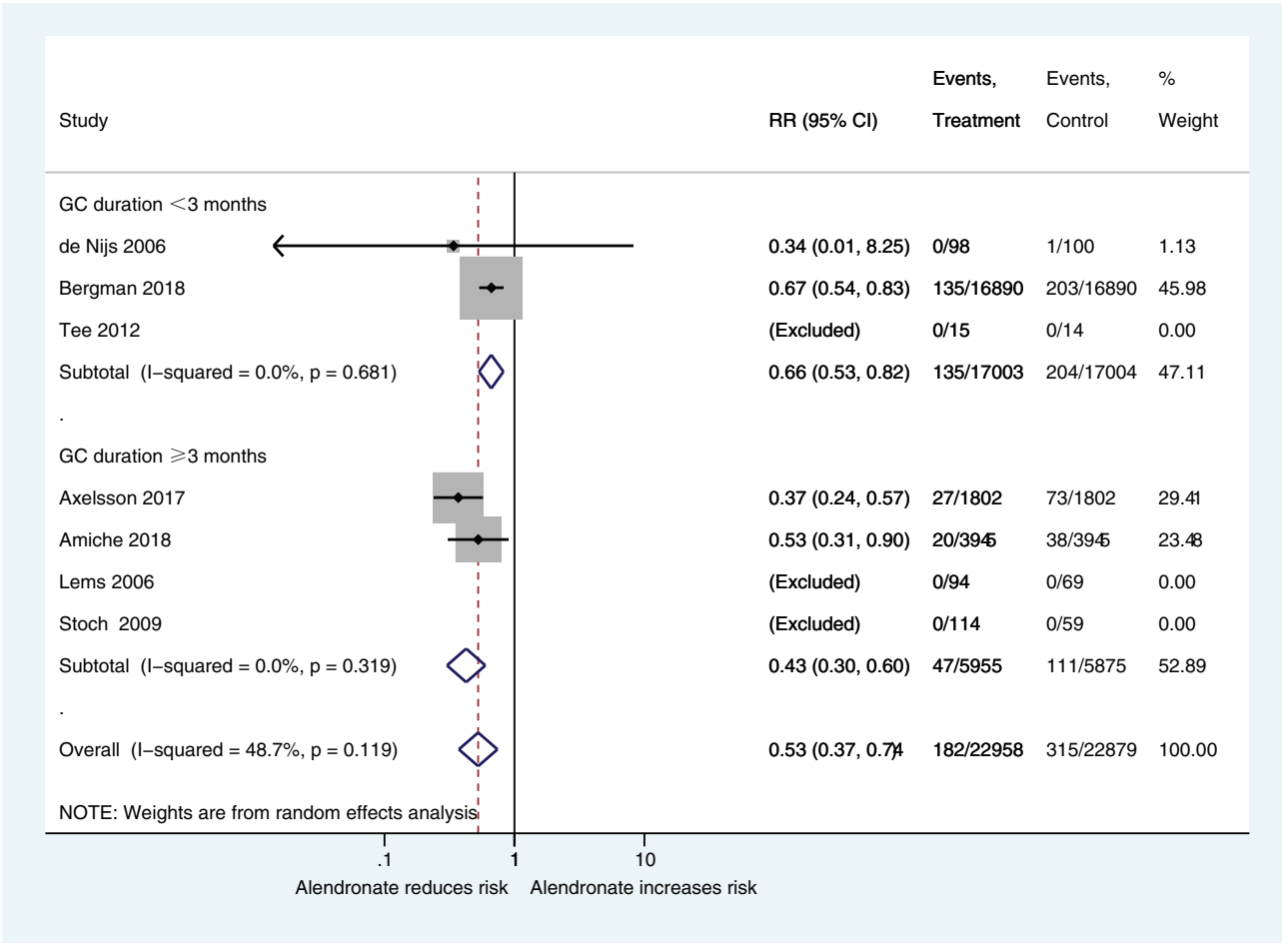

Figure 5. Subgroup meta-analysis stratified by GC duration for hip fractures.

are able to significantly increase lumbar spine BMD in patients with GIOP[39] and are also recommended for adults with no known osteoporosis or vitamin D deficiency to prevent fractures.[40]

Fifth, we failed to respectively assess the anti-fracture effectiveness of different doses of alendronate (ie., 5 mg/d, and 10 mg/d) due to their efficacy reported in combination in primary studies, and failed to assess whether there was an association between the anti-fracture efficacy of alendronate and proportion of baseline immunosuppressant use or 10-year fracture probability calculated by the Fracture Risk Assessment Tool due to the limited data available.

Last, our study tried to identify the factors affecting alendronate's efficacy, but failed to identify the factors affecting the efficacy of other first- or second-line agents (eg, risedronate, zoledronate, ibandronate, teriparatide, and denosumab)[41] for the prevention of GI fractures. Future studies are needed to fill this knowledge gap.

5. Conclusions

The findings in our study support that alendronate is used for the primary and secondary prevention of GI fractures, but do not support that alendronate is recommended as a first-line agent for patients receiving a low dose of GCs or patients with prevalent vertebral fracture. Studies with more specific subgroup analyses are needed to provide medical evidence for more specific patients.

Author contributions

Conceptualization: Liangliang Ding.
Data curation: Jinhao Lin, Hua Huang.
Formal analysis: Mei Qiu.
Methodology: Jinhao Lin, Hua Huang.
Resources: Kaikai Li.
Software: Kaikai Li.
Supervision: Kaikai Li.
Validation: Miao Zhang.
Visualization: Miao Zhang.
Writing – original draft: Mei Qiu.
Writing – review and editing: Liangliang Ding.

References

[1] Adami G, Saag KG. Glucocorticoid-induced osteoporosis: 2019 concise clinical review. Osteoporos Int 2019;30:1145–56.
[2] Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. N Engl J Med 2011;365:62–70.
[3] Weinstein RS. Glucocorticoid-induced osteoporosis and osteonecrosis. Endocrinol Metab Clin North Am 2012;41:595–611.
[4] Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.

[5] Qaseem A, Forciea MA, Mclean RM, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166:818–39.
[6] Buckley L, Guyatt G, Fink HA, et al. 2017 American college of rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol 2017;69:1521–37.
[7] Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev 2016;10:D1347.
[8] Amiche MA, Albaum JM, Tadrous M, et al. Fracture risk in oral glucocorticoid users: a Bayesian meta-regression leveraging control arms of osteoporosis clinical trials. Osteoporos Int 2016;27:1709–18.
[9] Kanis JA, Stevenson M, Mccloskey EV, et al. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 2007;11:1–231.
[10] Wang YK, Zhang YM, Qin SQ, et al. Effects of alendronate for treatment of glucocorticoid-induced osteoporosis: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97:e12691.
[11] Kan SL, Yuan ZF, Li Y, et al. Alendronate prevents glucocorticoid-induced osteoporosis in patients with rheumatic diseases: a meta-analysis. Medicine (Baltimore) 2016;95:e3990.
[12] Axelsson KF, Nilsson AG, Wedel H, et al. Association between alendronate use and hip fracture risk in older patients using oral prednisolone. JAMA 2017;318:146–55.
[13] Bergman J, Nordstrom A, Nordstrom P. Alendronate use and the risk of nonvertebral fracture during glucocorticoid therapy: a retrospective cohort study. J Clin Endocrinol Metab 2018;103:306–13.
[14] Amiche MA, Levesque LE, Gomes T, et al. Effectiveness of oral bisphosphonates in reducing fracture risk among oral glucocorticoid users: three matched cohort analyses. J Bone Miner Res 2018;33:419–29.
[15] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[16] Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929–36.
[17] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.
[18] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[19] O'Donnell S, Cranney A, Wells GA, et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev 2006;D5326.
[20] Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;D4523.
[21] Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[22] de Nijs RN, Jacobs JW, Lems WF, et al. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med 2006;355:675–84.
[23] Lems WF, Lodder MC, Lips P, et al. Positive effect of alendronate on bone mineral density and markers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. Osteoporos Int 2006;17:716–23.
[24] Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-induced osteoporosis intervention study group. N Engl J Med 1998; 339:292–9.
[25] Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001;44:202–11.
[26] Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol 2009;36: 1705–14.
[27] Tee SI, Yosipovitch G, Chan YC, et al. Prevention of glucocorticoid-induced osteoporosis in immunobullous diseases with alendronate: a randomized, double-blind, placebo-controlled study. Arch Dermatol 2012;148:307–14.
[28] Shane E, Addesso V, Namerow PB, et al. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med 2004;350:767–76.
[29] Tanaka Y, Mori H, Aoki T, et al. Analysis of bone metabolism during early stage and clinical benefits of early intervention with alendronate in patients with systemic rheumatic diseases treated with high-dose glucocorticoid: Early DIagnosis and Treatment of OsteopoRosis in Japan (EDITOR-J) study. J Bone Miner Metab 2016;34:646–54.
[30] Sambrook PN, Kotowicz M, Nash P, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. J Bone Miner Res 2003;18:919–24.
[31] Okada Y, Nawata M, Nakayamada S, et al. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol 2008;35:2249–54.
[32] Jensen TW, Hansen MS, Horslev-Petersen K, et al. Periarticular and generalised bone loss in patients with early rheumatoid arthritis: influence of alendronate and intra-articular glucocorticoid treatment. Post hoc analyses from the CIMESTRA trial. Ann Rheum Dis 2014;73:1123–9.
[33] Kendler DL, Marin F, Zerbini C, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2018;391:230–40.
[34] Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417–27.
[35] Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:4528–35.
[36] Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. J Bone Miner Res 2013;28: 1355–68.
[37] Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 2007;357:2028–39.
[38] Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;D1155.
[39] Homik J, Suarez-Almazor ME, Shea B, et al. Calcium and vitamin D for corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2000; D952.
[40] Bischoff-Ferrari HA, Bhasin S, Manson JE. Preventing fractures and falls: a limited role for calcium and vitamin d supplements? JAMA 2018;319:1552–3.
[41] Buckley L, Humphrey MB. Glucocorticoid-induced osteoporosis. N Engl J Med 2018;379:2547–56.