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

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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%. 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 and osteoporotic fractures are the most common serious adverse events which occur in patients receiving long-term or high doses of GCs. 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 and GIOP, 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 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 newly published to provide the newest evidence about alendronate for GIOP.
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. 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) GCs with a low dosage (<7.5 mg/day) or high dosage (≥7.5 mg/day) 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 alfalfacalcidol; 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).

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 multivariate 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. The search strategies 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, 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, 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. 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. 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 I². I² > 50% or P from Cochran Q test <.01 is considered as substantial heterogeneity. We performed meta-regression analysis to explore sources of heterogeneity for primary outcomes when I² 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. 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 | Adjuvant therapy | Sample size |
|----------|-------|-----------------|--------------|----------------|-------------|-----------------|-------------|
| 1[22]   | de Nijs 2006 | The outpatient clinics of 23 departments of rheumatology in the Netherlands | Yes | 18 | 5 | 2 | Calcium (mg/d) | 500 | 400 | 98 | 100 |
| 2[23]   | Lems 2006 | Netherlands, Belgium | No | 12 | 2 | 1 | Vitamin D (IU/d) | 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 | | 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 | | 800–1000 | 250–500 | 147 | 61 |
| 5[26]   | Stoch 2009 | USA | Yes | 12 | 5 | 2 | | 1000 | 400 | 114 | 59 |
| 6[27]   | Tee 2012 | Singapore | Yes | 12 | 5 | 2 | | 360 | 400 | 22 | 22 |
| 7[28]   | Axelsson 2017 | Sweden | Cohort study | 15.8 | 9 | – | Calcium | 87.5% | 87.5% | 1802 | 1802 |
| 8[29]   | Bergman 2018 | Sweden | Cohort study | 14.5 | 8 | – | Vitamin D | 78.3% | 78.3% | 16890 | 16890 |
| 9[29]   | Amiche 2018 | Canada | Cohort study | 12 | 6 | – | | NR | NR | 3945 | 3945 |
| 10[30]  | Shane 2004 | 390 at the Columbia-Presbyterian Medical Center and 42 at the Newark-Beth Israel Medical Center | Yes | 12 | 5 | 2 | Calcium | 945 | 1000 | 74 | 75 |
| 11[29]  | Tamaka 2015 | Japan | No | 12 | 2 | 1 | | NR | NR | 33 | 28 |
| 12[31]  | Sambrook 2003 | 4 Australian centers | No | 24 | 3 | 2 | | 600 | – | 64 | 64 |
| 13[31]  | Okada 2008 | Japan | No | 18 | 2 | 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.
Calcium or vitamin D daily for the duration of the study as adjuvant therapy.

3. Results
3.1. Characteristics of included studies
The workflow 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 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 3[12–14] 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, I² 41.8%), nonvertebral fractures (RR 0.67, 95% CI 0.54–0.82, I² 48.3%) and hip fractures (RR 0.53, 95% CI 0.37–0.74, I² 48.7%). No significant difference between 2 groups was observed in adverse events (RR 0.99, 95% CI 0.92–1.06, I² 3.5%), serious adverse events (RR 0.81, 95% CI 0.51–1.27, I² 29.3%) and tolerability (RR 0.62, 95% CI 0.38–1.01, I² 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 I² values suggested that it was essential to perform meta-regression analysis to explore sources of heterogeneity for primary endpoints since I² 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
coefficients, the RR of alendronate versus comparator treatment in preventing vertebral fractures probably decreased by 4.3% for 1 mg increase 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 $\geq 7.5$ 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 $\geq 5\%$ (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, $P$ 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
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 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 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 confirmed the anti-fracture efficacy of alendronate for the primary and secondary prevention of postmenopausal osteo-

### Table: subgroup meta-analysis stratified by GC dosage for vertebral fractures

| Study       | Event, Treatment | Event, Control | Weight |
|-------------|------------------|----------------|--------|
| GC dosage ≥7.5 mg/day | 0.38 (0.10, 1.40) | 3/96 | 8/100 | 6.76 |
| de Nijs 2006 | 0.10 (0.01, 0.90) | 1/143 | 4/59 | 2.76 |
| Adachi 2001 | 0.94 (0.48, 1.86) | 16/1802 | 17/1802 | 16.31 |
| Axelsson 2017 | 0.75 (0.52, 1.08) | 51/16890 | 68/16890 | 26.40 |
| Bergman 2018 | 0.54 (0.42, 0.71) | 80/3946 | 147/3946 | 29.69 |
| Amiche 2018 | 1.90 (0.36, 9.96) | 4/59 | 2/56 | 4.48 |
| Shane 2004 | 0.28 (0.06, 1.29) | 2/33 | 6/28 | 5.20 |
| Tanaka 2015 | 0.10 (0.01, 1.81) | 0/17 | 4/16 | 1.66 |
| Okada 2008 | (Excluded) | 0/114 | 0/59 | 0.00 |
| Stoch 2009 | (Excluded) | 0/15 | 0/14 | 0.00 |
| Tee 2012 | 0.61 (0.44, 0.86) | 157/23116 | 236/22969 | 93.27 |
| Subtotal (I-squared = 35.5%, p = 0.146) |  &nbsp; | &nbsp; | &nbsp; |
| GC dosage <7.5 mg/day | 3.09 (0.70, 13.66) | 9/70 | 2/48 | 5.39 |
| Lems 2006 | 0.32 (0.01, 7.66) | 0/64 | 1/61 | 1.34 |
| Sambrook 2003 | 1.56 (0.20, 12.02) | 9/134 | 3/109 | 6.73 |
| Subtotal (I-squared = 37.9%, p = 0.204) |  &nbsp; | &nbsp; | &nbsp; |
| Overall (I-squared = 41.8%, p = 0.079) | 0.65 (0.45, 0.96) | 166/23250 | 259/23078 | 100.00 |

**NOTE:** Weights are from random effects analysis.
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 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 from 18.1% 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.
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.
are able to significantly increase lumbar spine BMD in patients with GIOPI[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.

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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. Endocr Rev 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.
[11] Kan SL, Yuan ZF, Li Y, et al. Alendronate prevents glucocorticoid-induced osteoporosis. Arthritis Rheumatol 2017;69:1521–37.

[10] Wang YK, Zhang YM, Qin SQ, et al. Effects of alendronate for treatment of glucocorticoid users: a Bayesian meta-regression leveraging control arms of osteoporosis clinical trials. Osteoporos Int 2016;27:1709–18.

[9] Kanis JA, Stevenson M, Mcloskey EV, et al. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 2007;11:i–1–231.

[8] Amiche MA, Albuaum 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.

[7] Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97:e12691.

[6] Buckley L, Guyatt G, Fink HA, et al. 2017 American college of intern med 2017;166:818–39.

[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.

[4] Buckley L, Gayatt 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.

[3] Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev 2016;10:D1347.

[2] Amiche MA, Albuaum 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.

[1] Kanis JA, Stevenson M, Mcloskey EV, et al. Glucocorticoid-induced osteoporosis: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97:e12691.