Upper gastrointestinal safety and tolerability of oral alendronate: A meta-analysis

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Abstract. Osteoporosis (OP), which is a common bone disease associated with reduced bone mineral density and disordered bone microstructure, may result in an increased risk of bone fracture. The present study aimed to investigate the frequency of alendronate (Aln)-associated upper gastrointestinal tract adverse events (GIAEs) in postmenopausal women with OP. The following databases were searched in order to identify relevant studies: Medline (using PubMed as the search engine), Embase, the Web of Science and the Cochrane Central Register of Controlled Trials (up to December 2014). Studies were selected for inclusion if they were randomized, double-blind, placebo-controlled trials, which had investigated the safety of Aln versus a placebo for the treatment of postmenopausal women with OP. The primary outcomes of the included studies were total adverse events (AEs) and upper GIAEs, whereas individual upper GIAEs were considered as secondary outcomes. The general characteristics and outcomes of each study were abstracted by two independent researchers, and Review Manager 5.3 software was used for data syntheses and the meta-analysis. A total of nine studies, including 15,192 randomized patients, met the inclusion criteria and contributed to some or all of the meta-analysis outcomes. The Mantel-Haenszel method was used to calculate risk ratios, and their 95% confidence intervals (CI) were determined using either the fixed or random effects model, depending on the level of heterogeneity. The relative risk (95% CI) of AEs associated with Aln treatment, as compared with the placebo group, was 1.01 (0.97-1.06), and the relative risk (95% CI) of discontinued Aln treatment due to AEs was 1.04 (0.91-1.19). In addition, the relative risk (95% CI) of upper GIAEs was 1.02 (0.99-1.06), and the relative risk (95% CI) of discontinued Aln treatment due to upper GIAEs was 1.23 (0.97-56). In addition, these results remained robust to sensitivity analyses. The results of the present study suggested that Aln has a good GI tract tolerability, and that daily treatment with 10 mg Aln sodium does not increase the risk of GIAEs in postmenopausal women with OP.

Introduction

Osteoporosis presents a significant public health challenge, which contributes a substantial cost economically and in terms of morbidity and mortality. The disease is characterized by low bone mineral density and degeneration of the bone micro-architecture, which increases bone brittleness and fracture risk. Four key mechanisms appear to be crucially involved in the pathogenesis of this condition: i) Inhibition of osteoclast recruitment; ii) inhibition of osteoclastic adhesion; iii) shortening of the life span of osteoclasts due to earlier apoptosis; and iv) the inhibition of osteoclast activity. Bisphosphonates are the most widely available treatments for osteoporosis in postmenopausal women. Among these, alendronate (Aln), which has been used extensively and has the longest history in clinical practice, is recognized as a first-line drug for the treatment of OP (1-6). Previous studies have demonstrated that Aln is able to effectively reduce the risk of vertebral, non-vertebral, hip and wrist fractures (7-9). The safety and tolerability of Aln has previously been investigated in various randomized controlled trials (RCTs) and retrospective studies (10-18), and the majority of these have reported similar side effects, including gastrointestinal tract adverse events (GIAEs), for the Aln-treated and placebo-treated groups. It has been reported that oral administration of bisphosphonates, particularly those containing a nitrogen atom, may be accompanied by digestive tract disturbances (19). In addition, other bisphosphonates, as well as Aln, have been associated with GIAEs, which may be linked to reduced compliance (20-23). These findings suggest that Aln may cause GI tract disorders. Furthermore, oesophageal- and gastric-associated side effects are among the most common reasons for terminating bisphosphonate therapy (24).

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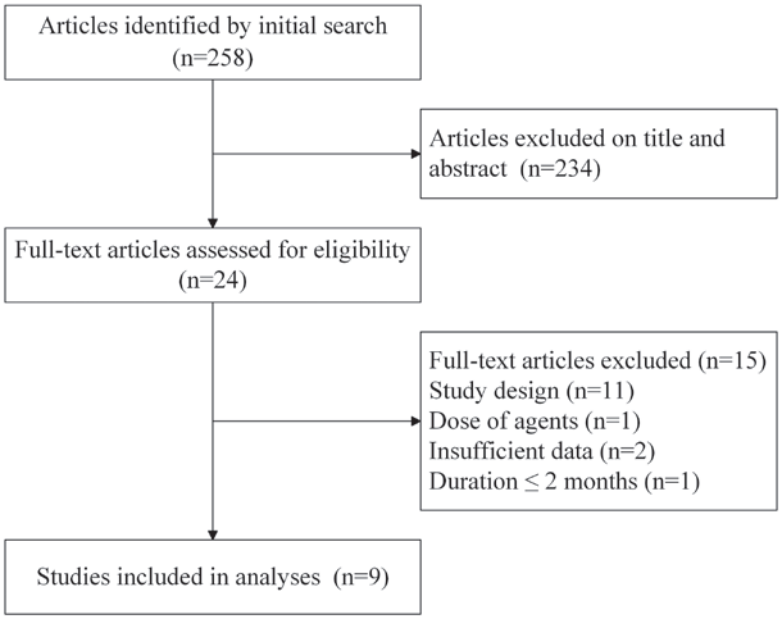

Figure 1. Flow diagram demonstrating the study selection process used in the present meta-analysis.

The present study conducted a meta-analysis of randomized, placebo-controlled trials abstracted from databases, in order to investigate the effects of Aln treatment on the risk of GIAEs in postmenopausal women with OP.

Materials and methods

Search strategy. The present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines for the meta-analysis of randomized controlled trials (25). A literature search for the purpose of identifying RCTs was performed. In order to identify eligible studies, the following databases were searched, with a date limit of December 30th, 2014: Medical Literature Analysis and Retrieval System Online, Medline (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com), the Web of Science (http://www.thomsonscientific.com.cn/productsservices/webofscience/) and the Cochrane Central Register of Controlled Trials (http://www.cochrane.org). The search terms used were as follows: 'Osteoporosis', 'alendronate' and 'gastrointestinal'. The search was limited to English-language publications and human trials.

Study selection. Studies were included in the present meta-analysis if they met the following criteria: i) They were randomized, double-blind, placebo-controlled trials analyzed by intention-to-treat (ITT); ii) the mean age of the trial participants was at a >50 years old baseline; iii) the study compared the safety or tolerability profile of Aln versus a placebo for the treatment of low bone mineral density or postmenopausal women with OP; and iv) the trial was >2 months. The exclusion criteria were as follows: i) The study included men or lasted for <2 months; ii) the study did not investigate upper GIAEs as an outcome; iii) duplicate publications; and iv) only the abstract was available.

Data abstraction. Data was tabulated by two independent investigators. A double-check procedure was performed in order to ensure the accuracy of the extracted data. The following information was extracted from each study: First author, publishing year, study design, patient number, treatment strategies, and outcomes. Methodological quality of the studies was assessed using Jadad scoring (26), in which studies were scored from 0-5, where a score of 0 corresponded to the lowest quality and a score of 5 represented the highest quality.

Statistical analysis. Analyses were conducted using the RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The safety profile of Aln was evaluated on the basis of the total number of reported adverse events (AEs), AEs resulting in discontinued Aln treatment, upper GIAEs, and GIAEs resulting in discontinued Aln treatment.

The Mantel-Haenszel method was used to calculate risk ratios (RRs), and their 95% confidence intervals (CI) were determined using either the fixed or random effects model, depending on the amount of observed heterogeneity. For heterogeneous outcomes (I^2>50%), a random-effects model meta-analysis was conducted, whereas, for homogeneous outcomes, a fixed-effects model meta-analysis was conducted. The effects of heterogeneity were quantified as follows: $I^2 = 100\% \times (Q-df)/Q$, where I^2 corresponded to the degree of inconsistency between the studies, and determined whether the total percentage of variation across the studies was due to heterogeneity or chance. I^2 ranged between 0 and 100%, where I^2 values of 25, 50 and 75% indicated low, moderate, and high estimates, respectively (27).

In order to detect publication bias, a sensitivity analysis was conducted using the trim and fill method or subgroup analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Identification and selection of studies. A total of 258 studies were retrieved in the initial search of electronic databases, of

Table I. Characteristics of the included studies.

First author Year/(ref)	Study design	Sample size (Aln/PBO)	Aln group age (mean±SD)	PBO group age (mean±SD)	Treatment	Duration (months)	Use of aspirin or NSAIDs [Aln(%)/PBO(%)]	Loss to follow up [Aln(%)/PBO(%)]
Adachi 2009/(27)	Multicenter, randomized, double-blind, placebo-controlled	291/147	65.4±10.5	65.7±9.9	70 mg Aln/week	3	27.8/27.9	18.6/11.6
Yan 2009/(28)	Multicenter, randomized, double-blind, placebo-controlled	280/280	65.2±6.5	64.7±5.9	70 mg Aln/week	12	N/A	18.9/15.0
Cryer 2005/(29)	Randomized, double-blind, placebo-controlled	224/230	64.6±10.0	65.8±9.9	70 mg Aln/week	6	43.8/44.8	13.8/13.5
Hosking 2003/(30)	Multicenter, randomized, double-blind, placebo-controlled	219/108	69.2±6.6	69.6±7.0	70 mg Aln/week for 12 months	12	N/A	21.5/17.6
Miller 2000/(31)	Multicenter, randomized, double-blind, placebo-controlled	88/84	67.0±11.0	67.1±10.1	70 mg Aln/week	2	33.0/29.8	No
Bauer 2000/(32)	Randomized, double-blind, placebo-controlled	3236/3223	68.6±6.2	68.7±6.1	5 mg Aln/day; 2 years later 10 mg/day	45	88.4/87.5	No
Pols 1999/(33)	Randomized, double-blind, placebo-controlled	950/958	62.8±7.5	62.8±7.4	70 mg Aln/week	12	N/A	8.9/13.2
Felsenberg 1998/(34)	Randomized, triple-blind, parallel group, placebo-controlled	219/223	64.1±6.7	63.5±7.5	70 mg Aln/week	12	N/A	15.1/14.8
Cumming 1998/(35)	Randomized, double-blind, placebo-controlled	2214/2218	67.6±6.2	67.7±6.1	5 mg Aln/day; 2 years later 10 mg/day	50	N/A	No

Aln, alendronate; PBO, placebo; SD, standard deviation; NSAID, nonsteroidal, anti-inflammatory drug; Ris, risedronate ; N/A, not applicable.

Table II. Quality assessment of the included studies (Jadad score).

First author (ref)	Random sequence generation	Appropriate randomization	Blinding of participant or personnel	Blinding of outcome assessors	Withdrawals and dropouts	Sum (Jadad score)	miTT
Adachi (27)	1	1	1	1	1	5	Yes
Yan (28)	1	1	1	1	1	5	Yes
Cryer (29)	1	1	1	1	1	5	Yes
Miller (31)	1	0	1	1	0	3	Yes
Bauer (32)	1	0	1	1	1	4	Yes
Felsenberg (34)	1	0	1	1	1	4	Yes
Cumming (35)	1	1	1	1	0	4	Yes
Pols (33)	1	0	1	1	1	4	Yes
Hosking (30)	1	1	1	1	1	5	Yes

Points were awarded as follows: Study described as randomized, 1 point; appropriate randomization, 1 point; subjects blinded to intervention, 1 point; evaluator blinded to intervention, 1 point; description of withdrawals and dropouts, 1 point. mITT, modified intention-to-treat.

which 234 were excluded on the basis of their title and/or abstract. Of the remaining 24 studies, a total of nine RCTs were selected for inclusion in the present meta-analysis following full text reviews (28-36). A flow chart of the study selection process is presented in Fig. 1.

Study characteristics. The characteristics of the included studies are presented in Table I. A total of 15,192 participants (7,721 in the Aln group and 7,471 in the placebo group) were included in the present meta-analysis; all of which were postmenopausal women (mean age range, 62.8-69.6 years), which had previously been diagnosed with a low bone density. All the studies were randomized, double-blind, placebo-controlled trials. Two of the studies (33,36) initially administered 5 mg Aln daily; however this was later increased to 10 mg daily, as the AEs associated with a 5 mg Aln sodium dose have been shown to be markedly similar to those associated with the 10 mg Aln sodium dose (37-39). As the commercial dose of Aln is 10 mg, the analyses only used the data from patients who had been treated with a 10 mg Aln dose.

Four studies (28,30,32,33) administered aspirin or a nonsteroidal anti-inflammatory drug (NSAID), to the two groups. In addition, four studies conducted a 1 year follow-up (29,31,34,35), whereas two studies had a follow-up at >1 year (33,36), and the remaining three studies had a follow-up at <1 year. In addition, four of the included studies (32-35) lacked appropriately described randomization, and three studies (32,33,36) lacked a description of drop-outs. All the studies claimed to apply ITT analysis. The level of evidence for each article was scored from 3 to 5, according to the Jadad quality score (Table II).

Total AEs. The risk ratio (95% CI) of AEs occurring in postmenopausal women treated with Aln, as compared with the placebo, was 1.01 (0.97-1.06), and this was not statistically significant (P>0.05; Fig. 2A). This outcome was attributed to heterogeneity among the included studies. A sensitivity analysis was conducted by dividing the studies into subgroups based on their duration; however, the heterogeneity remained and the results were not statistically significant. The risk ratio (95% CI) of discontinued Aln-treatment due to the occurrence of AEs, as compared with the placebo, was 1.04 (0.91-1.19), and this was not statistically significant (P>0.05; Fig. 2B). This outcome could not be attributed to heterogeneity among the studies. The sensitivity analysis demonstrated that this outcome could not be altered by omitting any single trial.

Upper GI AEs. The risk ratio (95% CI) of upper GIAEs occurring in postmenopausal women treated with Aln, as compared with the placebo, was 1.02 (0.99-1.06), and this was not statistically significant (P>0.05; Fig. 2C). The heterogeneity among all studies was insignificant. The sensitivity analysis demonstrated that the overall effect could not be altered by omitting any single trial. The risk ratio (95% CI) of the Aln-treatment of postmenopausal women being discontinued due to the occurrence of upper GIAEs, as compared with the placebo, was 1.23 (0.97-1.56), and this was not statistically significant (P>0.05; Fig. 2D). The heterogeneity among all studies was insignificant. The sensitivity analysis demonstrated that this outcome could not be altered by omitting any single trial.

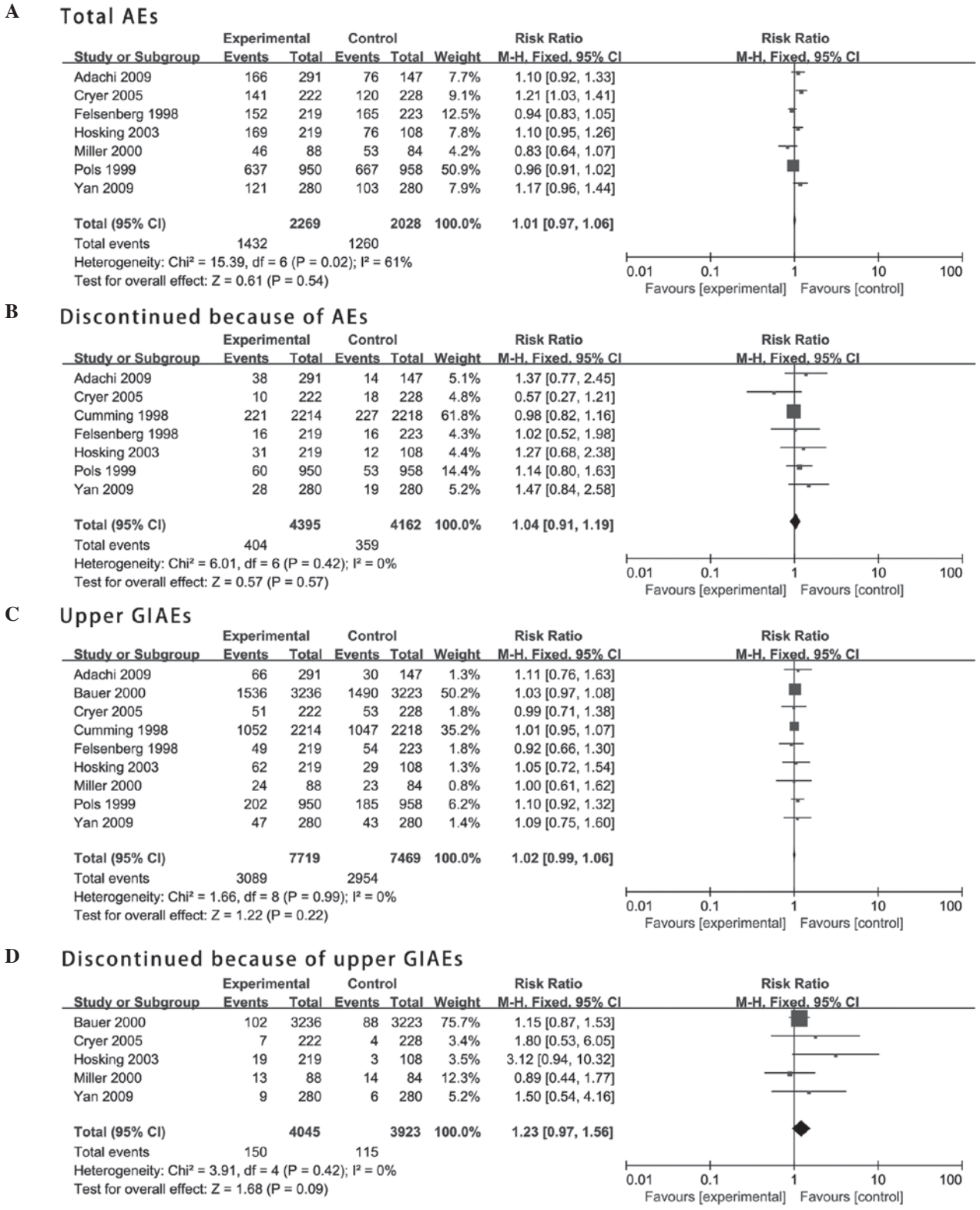

Figure 2. The relative risk of (A) AEs, (B) discontinued Aln treatment due to AEs, (C) upper GIAEs and (D) discontinued Aln treatment due to GIAEs in the Aln-treated groups, as compared with the placebo-treated groups of all included studies. AEs, adverse events; GIAEs, gastrointestinal adverse events; Aln, alendronate; M-H, Mantel-Haenszel method; CI, confidence interval.

Individual upper GIAEs. Individual upper GIAEs, including abdominal pain, nausea, dyspepsia, acid regurgitation, vomiting, gastroesophageal reflux and esophagitis, were the most common upper GIAEs reported among the studies. No significant differences in the incidence of individual GIAEs between the Aln-treated and placebo-treated groups were observed (Table III). The heterogeneity across the studies was insignificant. The sensitivity analysis demonstrated that this outcome could not be altered by omitting any single trial.

Table III. Patients with upper GIAEs.

Upper GIAE	No. of studies	No. (%) of patients		RR (95% CI)	P-value
		Aln	PBO		
Abdominal pain	7	910 (12.6)	877 (12.2)	1.04 (0.95-1.13)	0.41
Nausea	6	445 (8.9)	458 (9.2)	0.97 (0.86-1.10)	0.62
Dyspepsia	5	639 (13.4)	674 (14.1)	0.94 (0.86-1.04)	0.25
Acid regurgitation	5	467 (6.9)	445 (6.6)	1.05 (0.92-1.19)	0.47
Vomiting	5	136 (2.8)	130 (2.7)	1.04 (0.82-1.32)	0.72
Gastroesophageal reflux	4	81 (1.8)	88 (2.0)	0.91 (0.68-1.23)	0.55
Esophagitis	4	49 (0.8)	32 (0.5)	1.53 (0.98-2.38)	0.06

GIAE, gastrointestinal adverse events; Aln, alendronate; PBO, placebo; RR, risk ratio; CI, confidence interval.

Discussion

The present study conducted a meta-analysis of results from RCTs in the literature, in order to investigate the effects of Aln treatment on the risk of upper GIAEs in postmenopausal women with OP. A total of 258 studies were identified in the initial database search, of which nine RCTs met the inclusion criteria of the present study.

Previous studies have not identified a causative link between upper GIAEs and Aln treatment; however, the GI safety profile of bisphosphonates has been a concern in clinical practice (20-23). The present study enrolled a broader patient population and had a longer duration, as compared with previous trials. In addition, all the included studies were of a good quality. To the best of our knowledge, the present study is the first to evaluate upper GIAEs as a primary outcome; thus suggesting that our results would be more robust.

The duration of the studies included in the present meta-analysis ranged from 2 months to 4.2 years. Landfeldt *et al* (40) previously demonstrated that the incidence of upper GIAEs was inversely associated with the duration of treatment with Aln. However, some patients have demonstrated superior GI tolerability, whereas others have discontinued therapy after a shorter period of time. Therefore, it would be unreliable to only measure the incidence of upper GIAEs in patients who have persisted with therapy for a specific duration. In addition, if the analysis was restricted to patients who had remained on treatment for a specific duration, it would not be possible to generalize the results to the population of interest.

The treatment of patients with aspirin or NSAIDs was not included in the exclusion criteria (28,30,32,33), yet the presence of active GI tract disease, the need for anti-secretory therapy, and the use of aspirin or NSAIDs may have increased the risk of experiencing an upper GIAE in both the Aln-treated and placebo-treated groups (41). However, the effects of these risk factors were similar among the treatment groups.

The incidence of AEs was greater in the patients in the Aln-treated group, as compared with the placebo-treated group; however, the difference in the safety profile of Aln was not statistically significant between these groups. It should be noted that heterogeneity existed among the studies. A sensitivity analysis was conducted by dividing the studies into subgroups based on the study duration. In particular, the studies were divided into three subgroups: i) Duration <1 year; ii) duration = 1 year; and iii) duration >1 year. However, heterogeneity was still detected. Notably, the overall outcome could not be altered by omitting a single study.

The results of the present meta-analysis are consistent with those from previous studies (28-36), which also observed no significant difference in the frequency of upper GIAEs between placebo-treated and Aln-treated groups, and demonstrated that the GI safety and tolerability profile of Aln resembles the placebo (10,11). However, the present results contradict a previous study that suggested that Aln treatment may be associated with an increased risk of upper GIAEs in patients, as compared with no treatment (17). Furthermore, in the present study, the incidences of the primary individual upper GIAEs, including abdominal pain, nausea, dyspepsia, acid regurgitation, vomiting, gastroesophageal reflux and esophagitis, were not significantly different between the placebo- and Aln-treated groups. This is inconsistent with a previous study that suggested that patients treated with Aln developed specific GIAEs, including dyspepsia and upper abdominal pain (42).

Notably, oral bisphosphonates have fairly complex administration instructions (taken alone with 240 ml of water after fasting overnight, and remaining upright for at least 30 min), and poor compliance to these has previously been associated with an increased risk of GIAEs (11). This may explain why some studies have reported an increased risk of upper GIAEs in patients treated with Aln, and suggests that patients should strictly adhere to the treatment instructions when taking Aln.

The present study has some limitations: Firstly, the demographic was restricted to postmenopausal OP, and thus the results may not be extrapolated to patients with other conditions; secondly, although the database searches were extensive, we cannot be entirely sure that all relevant articles were included; and thirdly, the analysis was only based on published data.

In conclusion, the results from the present meta-analysis suggested that daily treatment with 10 mg Aln sodium was

not associated with an increased incidence of GIAEs, thus suggesting that Aln may be considered safe for the treatment of postmenopausal women with OP.

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