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ORIGINAL ARTICLE

Oral bisphosphonates reduce the risk of clinical fractures in glucocorticoid-induced osteoporosis in clinical practice

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Abstract
Summary This study aims to estimate bisphosphonate effectiveness by comparing fracture incidence over time on therapy in glucocorticoid-induced osteoporosis (GIO). From this observational study, alendronate and risedronate decreased clinical vertebral and nonvertebral fractures over time. The effectiveness of each bisphosphonate is consistent with their efficacies demonstrated on surrogate markers in randomized controlled trials (RCTs).
Introduction This study aims to estimate bisphosphonate effectiveness by comparing fracture incidence over time on therapy with fracture incidence during a short period after starting a therapy.
Methods The study population was a subgroup of a larger cohort study comprising two cohorts of women aged ≥65 years, prescribed with alendronate or risedronate. Within the two study cohorts, 11,007 women were identified as having received glucocorticoids. Within each cohort, the baseline incidence of clinical fractures at nonvertebral and vertebral sites was defined by the initial 3-month period after starting therapy. Relative to these baseline data, we then compared the fracture incidence during the subsequent 12 months on therapy.
Results The baseline incidence of clinical nonvertebral and vertebral fractures was similar in the alendronate cohort (5.22 and 5.79/100 person-years, respectively) and in the risedronate cohort (5.51 and 5.68/100 person-years, respectively). Relative to the baseline incidence, fracture incidence was significantly lower in the subsequent 12 months in both cohorts of alendronate (33 % lower at nonvertebral sites and 59 % at vertebral sites) and risedronate (28 % lower at nonvertebral sites and 54 % at vertebral sites).
Conclusion From this observational study not designed to compare drugs, both alendronate and risedronate decreased clinical vertebral and nonvertebral fractures over time. The reductions observed in fracture incidence, within each cohort, suggest that the effectiveness of each bisphosphonate in clinical practice is consistent with their efficacies demonstrated on surrogate markers in randomized controlled trials.

Keywords Bisphosphonates · Clinical fractures · Glucocorticoid-induced osteoporosis · Risk reduction

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Introduction

Long-term oral use of glucocorticoids is very common with 1 % of the general population and up to 2.5 % of those aged

70–79 years on therapy [1, 2]. Glucocorticoid-induced osteoporosis (GIO) is the primary form of secondary osteoporosis.

The pathophysiology of GIO is unique because it combines drug effects and those of the related inflammatory disease, alterations of bone and muscle tissues, and a rapid decrease in bone formation together with an increase in bone resorption. Therefore, glucocorticoid use leads to excessive bone fragility with a rapid dose-dependent increase in fracture risk (especially at vertebral sites) within a few months of therapy initiation, and a partial reversible pattern in the months following cessation of therapy [2]. In addition, cohort studies have shown that there is no safe threshold because fracture risk increases even with daily doses lower than 7.5 mg/day prednisolone equivalent, regardless of age or sex [3].

Management of GIO has improved over the years with the development of densitometry and the use of bisphosphonates for both prevention and treatment of GIO [4]. However, bisphosphonate effectiveness in these situations has only been evaluated in randomized controlled trials (RCTs) conducted in small groups of patients using only surrogate markers, such as bone mineral density (BMD) and bone turnover markers. Low fracture risk at baseline and short treatment duration precluded the demonstration of any positive effects on fragility fracture incidence as too few events occurred in most studies. Only post hoc analysis combining two studies evaluating risedronate for the prevention of GIO in patients receiving glucocorticoids for <3 months and for the treatment of GIO in patients receiving glucocorticoids for >6 months, showed a 70 % reduction in vertebral fracture incidence [5, 6].

Therefore, observational studies are a good opportunity to further evaluate bisphosphonate effectiveness in reducing clinical fractures [7–10], specifically in GIO treatment. To avoid some of the limitations in interpreting data from medical records without knowing differences in baseline fracture risk, we have shown that an approach of directly measuring the baseline risk of an outcome within patient populations may be applicable to the study of bisphosphonates [11]. Indeed, changes in bone quality take time and fracture reductions following initiation of bisphosphonates have not been noted earlier than 6 months after the start of therapy within post hoc, pooled analyses of clinical trials [12, 13]. Hence, we proposed to estimate bisphosphonate effectiveness by comparing fracture incidence over time on therapy, to fracture incidence during a short period after starting therapy.

For the current study, administrative billing data were used to follow three cohorts of women aged ≥65 years who had received 450 mg prednisone equivalent pills within ±90 days of cohort entry, after starting therapy either on alendronate, ibandronate, or risedronate. Within each cohort, the baseline incidence of clinical fractures at the hip, vertebral, and nonvertebral sites was defined by the initial 3-month period after starting therapy. Relative to these baseline rates, we then compared the fracture incidence during the subsequent 12 months on therapy.

Materials and methods

Data source

Computerized records of administrative billing data provide a convenient data source for studying drug use and outcomes in large populations. Such databases provide patient-level data of: (a) inpatient and outpatient services specified by diagnoses codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); (b) retail and mail-order pharmacy dispensations specified by national drug codes; and (c) demographic information including sex, age, and dates of health plan coverage in data source. The data for the current study, inclusive of January 2000 to December 2007, originated from two sources: Ingenix Lab/Rx (Eden Prairie, MN, USA) and Medstat MarketScan (Ann Arbor, MI, USA). In 2005, the number of women aged ≥65 years in these mutually exclusive data sources was 1.4 million in Medstat and 0.4 million in Ingenix. Geographically, half of the patient population was located in Michigan, California, Florida, Ohio, Georgia, and Texas, with the other 44 states comprising the remaining half.

Study population

The study population is a subgroup of a larger cohort study recently published [11], which consisted of three cohorts of women aged ≥65 years prescribed the oral bisphosphonates alendronate, risedronate, or ibandronate. Within the three study cohorts of the original publication, those with glucocorticoid use were identified. Glucocorticoid use was defined as receiving 450 mg prednisone equivalent pills within ±90 days of cohort entry, an approximation of the American College of Rheumatology (ACR) guideline of 5 mg/day prednisone for ≥90 days. This threshold was arbitrary, but we considered that ACR guidelines were a clinically relevant cut-point. It has to be kept in mind that even though claims data provided a good indicator whether ACR guidelines were met, they provided minimal fine detail on the dosing of glucocorticoids. Apart from rheumatoid arthritis, we had no information on the baseline diseases that induce the prescription. Subjects entered a cohort on the date of their initial filled prescription for alendronate 70 mg/week or risedronate 35 mg/week. Market introduction was on November 2000 for the alendronate cohort and May 2002 for the risedronate cohort. An attempt was made

to include a cohort that took ibandronate 150 mg/month during the time period of market introduction through to December 2006, but there were too few subjects (n=822) and less than 10 fractures were recorded during the 15-month period. Therefore, we considered the data from this cohort as insufficiently reliable. Consistent with prior studies [7, 9, 10, 14], the initial bisphosphonate prescription was defined by a subject having ≥6 months of prior coverage in the data source without any other bisphosphonate use (e.g., another bisphosphonate type or dose). After 6 months without any bisphosphonate use, a subject was allowed to enter a new cohort (i.e., a subject could be in more than one cohort); 1 % of the alendronate cohort and 4 % of the risedronate cohort were previously included in another cohort.

In addition, the study subjects were required to: (a) be women aged ≥65 years to provide a study population similar in age to that of the RCTs and for which clinical fractures are likely to be related to osteoporosis [15]; (b) have ≥3 months of coverage in the data source after cohort entry in order to provide minimum follow-up; and (c) have no diagnosis of malignant neoplasm (ICD-9-CM codes 140–208) or Paget's disease (ICD-9-CM code 731.0) within 6 months prior and 3 months post-cohort entry to maximize the probability that subjects were being treated for GIO.

History of prior fracture was defined by any clinical fracture diagnosis at the hip, wrist, humerus, clavicle, pelvis, leg, or vertebrae in the 6 months prior to cohort entry. A diagnosis of rheumatoid arthritis was based on any inpatient or outpatient diagnosis (ICD-9-CM code 714.0) within 6 months prior and 3 months post-cohort entry. Risk factors not available in the data source included BMD, body mass index, current smoking, alcohol consumption, and family history of fracture.

Fracture outcomes

After subjects entered a cohort, each was followed to identify three outcomes: a new hip fracture, a new nonvertebral fracture, or a new clinical vertebral fracture. During follow-up, a subject was counted only once for each type of fracture. Hip fractures were defined by an inpatient diagnosis at the hip (ICD-9-CM codes 820 and 733.14). Nonvertebral fractures were inclusive of inpatient diagnosis at the hip, and inpatient or outpatient diagnosis at the wrist (ICD-9-CM codes 813 and 733.12), humerus (ICD-9-CM codes 812 and 733.11), clavicle (ICD-9-CM code 810), pelvis (ICD-9-CM code 808), and leg (ICD-9-CM codes 821, 823, 733.15, and 733.16). Clinical vertebral fractures were defined by either inpatient or outpatient diagnosis at vertebral sites (ICD-9-CM codes 805.2, 805.4, 805.8, and 733.13). New fractures were defined as a fracture at each body site for which there was no fracture at that same site in the 6 months before cohort entry. To increase the probability of only including osteoporotic-related fractures, we excluded likely traumatic fractures by eliminating diagnoses of an open fracture or of a documented cause of injury other than an accidental fall (E-code of E880–E888). These exclusions removed <10 % of fracture outcomes.

Follow-up

All subjects contributed 3 months of follow-up after cohort entry, during which the baseline fracture incidence was calculated. The denominator was the sum of observation time for all subjects within a cohort during the 3 months. The numerator was the number of subjects with a new fracture during 3 months.

After 3 months of follow-up, subsequent observation was available for subjects through to December 2007 unless their individual coverage ceased in the data source (Fig. 1a). The fracture incidence was calculated for the subsequent 12 months of therapy. All subjects who had received a sufficient quantity of pills (of the same bisphosphonate type initiated at cohort entry) to provide for a medication possession ratio (MPR) of ≥80 % at the end of 3 months were followed into the subsequent 3-month period (Fig. 1b). The level utilized for the MPR has been frequently suggested to provide a high level of therapeutic effectiveness for bisphosphonates [16–23]. Subjects were followed until the end of this 3-month period or the end of their coverage in the data source. The same process was applied at the end of 6, 9, and 12 months after cohort entry. For the calculation of incidence, the denominator was the sum of observation time during follow-up preceded by a MPR of ≥80 %. The numerator included the number of subjects with a new fracture, preceded by a MPR of ≥80 %, akin to the previous study [14].

Statistical analysis

A simple ratio was used to compare the incidence of fractures between the initial 3 months of therapy and the subsequent 12 months of therapy. Poisson regression was used to compute the 95 % confidence intervals around the ratio. This study design was used for controlling confounding instead of statistical analysis. The primary analysis was within cohorts. Hence, the patients served as their own control. No age-adjusted regression was performed, since age had the same effect on all subjects across the study and such an adjustment made no difference.

Results

Cohort characteristics

Of the 210,157 patients initiating bisphosphonates and comprising the original cohort [11], a total of 11,007 received

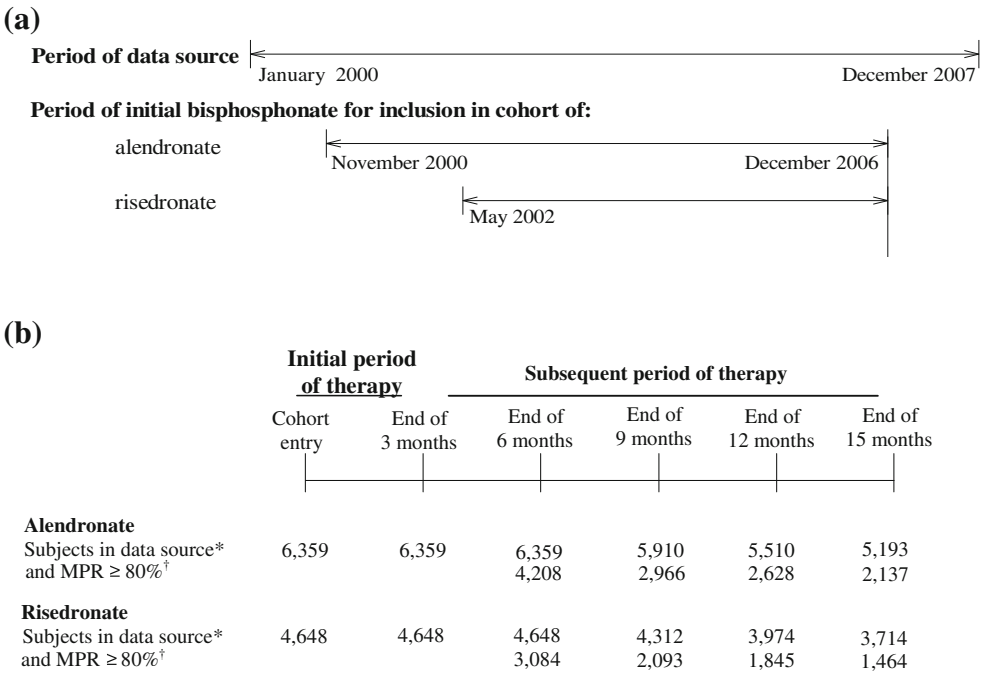

Fig. 1 Time period for cohort identification (**a**) and follow-up (**b**) for measure of fracture incidence for alendronate and risedronate. *Asterisk* indicates percentage of subjects who entered cohort that remained in data source after 12 months. *Dagger* indicates percentage of subjects remaining in data source that maintained high compliance to therapy (MPR≥80 %). *MPR* medication possession ratio

glucocorticoid (alendronate, n=6,359 [5 %] and risedronate, n=4,648 [6 %]) (Fig. 1b). The data source provided a record of health care utilization for ≥1 year after initial bisphosphonate prescription for >80 % of each cohort (Fig. 1b). Of those subjects in the data source for >1 year, between 39 % and 69 % of the cohorts were highly persistent to therapy, i.e., maintained a MPR of ≥80 %. The characteristics of the cohorts receiving either alendronate or risedronate are presented in Table 1.

Table 1 Characteristics of baseline fracture risk by study population

	Alendronate (n=6,359)	Risedronate (n=4,648)
Mean age at study entry (years)	75	76
Aged ≥75 years (%)	52	55
Clinical fracture[a], 6 months before study entry (%)	11	11
Glucocorticoid use at study entry (%)	100	100
Rheumatoid arthritis diagnosis at study entry (%)	16	21
Prior bisphosphonate use[b] (%)		
6 months before study entry	0	0
1 year	4	5
2 years	6	11
3 years	7	16
5 years	10	20

[a] Fracture diagnosis at the hip, clavicle, wrist, humerus, leg, pelvis, or vertebral sites

[b] Use of any bisphosphonate (e.g., daily formulations or other specified bisphosphonate) preceding study entry

Longitudinal incidence of fractures

After the first 3 months of therapy, the incidence of nonvertebral fractures and clinical vertebral fractures was observed in the subsequent 12 months for those subjects who were compliant with therapy. Numbers of hip fractures were too small to allow specific analysis. Relative to the fracture incidence during the initial 3 months of therapy, the incidence of nonvertebral fractures and of clinical vertebral fractures were significantly lower in the subsequent 12 months in both alendronate and risedronate cohorts (p<0.05) (Table 2). Because there were many hypothesized differences between those patients who started alendronate vs. risedronate, we did not perform a comparison between cohorts. Actually, with all the possible differences in mind, it is interesting to observe that the rates of nonvertebral and vertebral fractures during the initial 3 months for both alendronate and risedronate were very similar (Table 3). These similar baseline rates suggest that the two cohorts were of similar underlying fracture risk.

Discussion

The effect of oral bisphosphonate alendronate and risedronate in the treatment of corticosteroid-induced osteoporosis has been evaluated in three double-blind prospective controlled phase 3 trials [5, 6, 24]. These 12- to 24-month trials have been conducted in limited populations of 142 to 290

Table 2 Incidence of clinical fractures in the 3 months after starting therapy and subsequent 12-month period on therapy for glucocorticoid users

	Baseline: 3-month period after starting therapy			Follow-up: subsequent 12-month period on therapy			Ratio (95 % CI) of fracture incidence for follow-up/ baseline
	No. of subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	No. of subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	
Alendronate (n=6,359)							
Nonvertebral	83	1,590	5.22	100	2,846	3.51	0.67 (0.50, 0.90)*
Vertebral	92	1,590	5.79	67	2,846	2.35	0.41 (0.30, 0.56)*
Risedronate (n=4,648)							
Nonvertebral	64	1,162	5.51	79	2,000	3.95	0.72 (0.52, 1.00)*
Vertebral	66	1,162	5.68	52	2,000	2.60	0.46 (0.32, 0.66)*

CI confidence interval
*$p<0.05$

patients of men and pre- and postmenopausal women, in patients initiating corticosteroids [5], receiving corticosteroids [6], or both [24]. Morphometric vertebral fracture incidence in control groups has ranged from 6.8 % over 2 years [24], to 15 % [6] and 17.3 % [5] over 1 year, confirming severity of this type of osteoporosis. A nonsignificant reduction in the incidence of vertebral fractures has been shown with both drugs and this reduction was statistically significant when different doses of bisphosphonate used in the trials were combined [6, 24] or when treatment and prevention studies were combined [25]. Numbers of nonvertebral fractures were small and no reduction in nonvertebral fracture incidence was seen in any of these trials.

Therefore, this observational study supports, for the first time, that the anticipated benefits of oral bisphosphonate use in the treatment of GIO based on surrogate markers, such as BMD and post hoc analysis in RCTs, were actually observed in clinical practice with reduction in the incidence of clinical vertebral fractures. These data are also important because they confirm the reliability of such bridging studies in GIO recommended by authorities when a drug has previously demonstrated effectiveness in reducing fracture risk in postmenopausal osteoporosis [26]. This is applicable as well for the weekly administration of both oral bisphosphonates that were used in this population, whereas antifracture efficacy in postmenopausal osteoporosis was demonstrated with daily administration.

Of note is that our data showed a significant reduction in the risk of nonvertebral fractures. Epidemiologic studies have also reported an increased risk in nonvertebral fractures under glucocorticoid use [3, 27], and the high incidence of these events in our cohorts is consistent with these results. Furthermore, as these events represent a large part of GIO-related burden for both patient quality of life and the health care system, the observed reduction in nonvertebral fracture risk in our study support a simulation model suggesting that prevention of GIO is cost-effective in patients at high risk [28].

As previously reported in a postmenopausal osteoporosis study [11], change in fracture incidence over time within a cohort may be utilized likewise to measure bisphosphonate effectiveness in GIO. Patients included in this study were using a glucocorticoid for ≥90 days and it has been shown that fracture risk increased rapidly within 3 to 6 months after treatment initiation [2]. Therefore, the baseline fracture incidence during the initial 3 months of starting therapy

Table 3 Number of clinical fractures for each 3-month period after starting therapy and subsequent 12-month period on therapy for glucocorticoid users

Alendronate		Subjects (n)	Person-years (n)	NV fractures (n)	V fractures (n)	Nonvert rate (%)	Vert rate (%)
	Quarter 1	6,359	1,590	83	92	5.22	5.79
	Quarter 2	4,208	1,022	43	28	4.21	2.74
	Quarter 3	2,966	699	21	15	3.00	2.15
	Quarter 4	2,628	620	19	16	3.06	2.58
	Quarter 5	2,137	505	17	8	3.37	1.58
Risedronate							
	Quarter 1	4,648	1,162	64	66	5.51	5.68
	Quarter 2	3,084	746.5	39	19	5.22	2.55
	Quarter 3	2,093	489.5	18	16	3.68	3.27
	Quarter 4	1,845	426.9	12	8	2.81	1.87
	Quarter 5	1,464	336.6	10	9	2.97	2.67

adequately reflected the underlying risk of the cohort with levels of incidence in the expected range, confirming that our population was at high risk of fracture [29].

There are limitations in the interpretation of results from observational studies using administrative databases; these include missing information on some fracture risks and no X-ray confirmation of fracture with potential for the misclassification of outcomes. It is known from a prior study that misclassification does not depend on the cohort and that the proportion of fracture claims confirmed by chart review to be a fracture was highest for the hip relative to other fracture sites [30]. Another limitation of our study design is that a significant and measurable biological response to bisphosphonate occurs within the first 3 months of therapy. However, any trend in fracture incidence reduction has never been observed in such a short period of time in any clinical trial evaluating bisphosphonates in the treatment of osteoporotic patients. Therefore, the limitation of a putative early decrease in fracture incidence was conservative, as we used this period as the reference period and it might have only blunted the difference with the subsequent 12-month period of therapy. Finally, the information provided by the database cannot answer the question of whether patients receiving glucocorticoids during the first 3 months, but then discontinuing therapy during the next 12 months, had a reduction in fracture risk related to bisphosphonate therapy or not. Epidemiologic data from other databases (2,3) suggest that the increase in fracture risk occurs within the first 3 months of treatment and then remains stable over the glucocorticoid therapy period. More importantly, the decrease in fracture risk following end of glucocorticoid therapy usually takes longer as the risk is still significantly higher within the second year than the one prior therapy.

In conclusion, from this largest observational study conducted in a population using glucocorticoids, the longitudinal analyses indicated that alendronate and risedronate decreased clinical vertebral and nonvertebral fractures over time. The study was not designed to compare both drugs and these apparent reductions in fracture incidence over time within each cohort, although numerically different, fell within the same confidence intervals. These data suggest that the effectiveness of each bisphosphonate in clinical practice has been consistent with their efficacies demonstrated on surrogate markers in RCTs.

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Conflicts of interest Dr. Thomas reports receiving consulting or advisory committee fees from Amgen, Lilly, Merck, Novartis, Warner Chilcott, Roche/GlaxoSmithKline, and Servier; and grant support from Lilly, Merck, Novartis, and Servier. Dr. Ringe reports receiving advisory committee fees from Amgen, Merck, and Servier. Dr. Gold reports receiving consulting or advisory committee fees from Amgen, Eli Lilly, GlaxoSmithKline, Merck, and Sanofi; and serves on speaker's bureaus for Amgen, Eli Lilly, Warner Chilcott, Roche, and Sanofi. Dr. Abelson has no conflict of interest to declare. Dr. Horlait and Atlan are employees of Warner Chilcott, and Dr. Lange was an employee of Procter & Gamble.

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