Incidence of Gastrointestinal Events Among Bisphosphonate Patients in an Observational Setting

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Abstract

Objective: To compare the incidence of gastrointestinal (GI) events among patients initiating alendronate or risedronate therapy.

Study Design: Retrospective observational study of an administrative claims database.

Methods: Patients aged 65 years and older who received a new prescription for risedronate (n = 865) or alendronate (n = 5255) between November 1, 2000, and May 31, 2002, were selected for analysis. Preexisting GI conditions and medication use for the 2 treatment groups in the 6 months before initiation of bisphosphonates were also determined. A Mantel-Haenszel relative risk estimate was used to compare the incidence of GI events within the first 4 months of treatment.

Results: In both the alendronate and risedronate treatment groups, the mean age was approximately 76 years and 93% were female. Treatment groups had a similar overall health status at baseline with the exception that proportionally more individuals who initiated risedronate had preexisting GI conditions compared with alendronate users (13.8% vs 11%, odds ratio = 0.77, $P = .02$). In the first 4 months following initiation of treatment, 8.2% of alendronate patients and 5.5% of risedronate patients had a documented GI-related event. Adjusting for age, sex, preexisting GI conditions, and number of concomitant medications in the pretreatment period, the alendronate patients exhibited a 44% higher risk of GI events compared with risedronate patients (relative risk = 1.44; 95% confidence interval, 1.03-2.00; $P = .03$).

Conclusion: This analysis of administrative claims from a large managed care database supports a difference between alendronate and risedronate with respect to GI tolerability in the first 4 months of therapy.

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The bisphosphonate therapeutic class has become an important group of medications for the prevention and/or treatment of postmenopausal and glucocorticoid-induced osteoporosis.

Risedronate and alendronate are both nitrogen-containing compounds, but alendronate is a second-generation bisphosphonate and risedronate is a third-generation bisphosphonate with a nitrogen atom that forms part of a pyridine ring.[1] Structural differences affect not only the antiresorptive potency of these compounds, but also the nature and extent of side effects, with the gastrointestinal (GI) tract drawing the most concern.[1,2] Although the labels of both alendronate and risedronate instruct patients to remain upright for at least 30 minutes after taking the tablet (to reduce the potential for esophageal/gastric irritation), the clinical data suggest that GI side-effect profiles of the 2 products may be different.

Data from the pivotal randomized controlled clinical trials of alendronate suggested that the drug was well tolerated and had no greater clinical evidence of adverse effects than placebo, although patients with certain preexisting GI problems (eg, peptic ulcer disease or dyspepsia) were excluded,[3-5] as were those recently treated with agents that irritate the GI tract.[3] Soon after alendronate's release, an unexpectedly higher number of cases of esophagitis and esophageal strictures were encountered when the drug was prescribed to the general population, which resulted in changes to the alendronate label.[1,2] In the pivotal trials, risedronate was well tolerated, showing an incidence of side effects similar to placebo.[6-10] These trials included patients with preexisting and ongoing GI conditions. A pooled analysis of the tolerability experiences of more than 10 000 patients (>98% postmenopausal women) from the risedronate clinical trials demonstrated that the incidence of upper GI events was similar to

placebo, even in subpopulations with underlying upper GI disease, nonsteroidal anti-inflammatory drug (NSAID) use, or acid-secretion blocker use.[11]

Several endoscopy studies have examined the effect of either alendronate or risedronate compared with placebo or aspirin-treated patients.[12-19] Only 2 published studies were designed to make direct comparisons between alendronate and risedronate (at the dose indicated for osteoporosis). Lanza et al randomly assigned healthy, postmenopausal women to treatment with risedronate (5 mg/day) or alendronate (10 mg/day) for 2 weeks.[20]

Esophagogastroduodenoscopy was performed after 7 and 14 days of dosing, and results showed that risedronate was associated with a significantly lower incidence (4.1%) of gastric ulcers than alendronate (13.2%). Similar results were found by Thomson et al where gastric ulcers were observed in 6% of the risedronate users and 12.1% of the alendronate users, supporting a notable difference between risedronate and alendronate with respect to GI irritation.[21] This endoscopy research is suggestive of a difference in GI irritation between the 2 drugs in selected clinical populations, but the studies were limited by short duration, small sample sizes, and surrogate measures of intolerance. Additional supporting evidence would be advantageous, and observational database analyses could provide perspective on the GI profiles of both alendronate and risedronate in a population-based setting.

The purpose of this retrospective analysis is to examine the differences between alendronate and risedronate patients with respect to GI conditions occurring before and after the initiation of bisphosphonate treatment in a managed care setting.

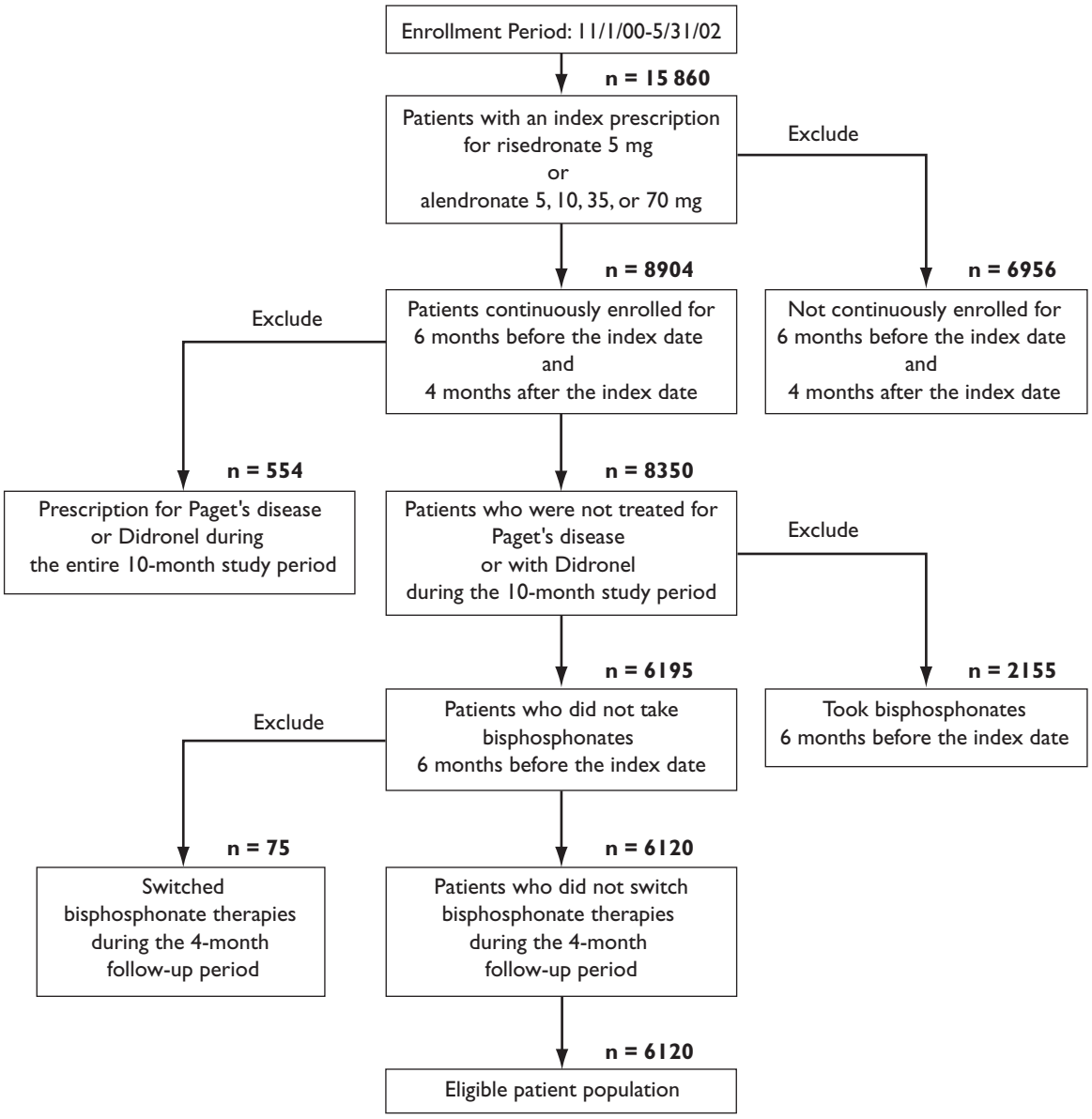
Methods

Database Description. We conducted a retrospective cohort study among patients with medical and pharmacy claims contained in a proprietary administrative claims database.[22] This database contains longitudinal data, representing healthcare services from professional, facility, and outpatient pharmacy claims and enrollment data, and has been used extensively for more than 10 years to conduct retrospective studies.[23-28] These services are provided through health maintenance organizations, preferred provider organizations, and various specialty products to approximately 3 million members annually. The plans cover a wide geographic distribution, with members residing in more than 20 states.

Study Population. Patients selected for the present study were women and men 65 years of age and older. All had a new prescription ("index" prescription) for alendronate (5, 10, 35, or 70 mg) or risedronate (5 mg) between November 1, 2000, and May 31, 2002 (**Figure**). Eligible patients were required to have medical and pharmacy benefits for the entire study period. Patients with a bisphosphonate prescription in the 6 months before the index date were not considered to be new users and were therefore not included in the analysis. Although patients were not required to have a diagnosis of osteoporosis, all patients with a Paget's disease *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code (731.0) were excluded from the analysis. Patients taking risedronate 30 mg and patients taking alendronate 40 mg were also considered to be Paget's disease patients and were not included in the study. Finally, individuals who switched products during the study period (ie, risedronate to alendronate or vice versa) were excluded. These switchers represented less than 5% of the study population.

Because weekly alendronate was commercially available during the study period (and weekly risedronate was not), consideration was given to combining weekly and daily alendronate for the analyses. To determine if this was appropriate, alendronate patients were initially excluded if they switched from daily to weekly or vice versa. Among the remaining individuals, weekly alendronate patients were compared with daily alendronate patients on the basis of GI events in the follow-up period. The 2 groups showed no significant difference in incidence of GI events, with 8.3% of the alendronate weekly and 7.6% of the alendronate

Figure. Flowchart of Patient Selection and Criteria Process



daily patients having a diagnosis code for a GI-related event (relative risk [RR] = 1.10, P = .40). Therefore, the decision was made to combine all alendronate users in the analysis, including those who switched dose strength during the treatment period.

Study Period. The pretreatment period was defined as the 6-month period before initiating treatment with the index therapy. The 4-month period after the index prescription was considered to be the treatment period. Rates of GI-related adverse events tend to be highest in the first few months of therapy, thus a 4-month treatment period was optimal for capturing the majority of events without compromising sample size.[29]

GI Health. In both the pretreatment and treatment periods, patients were assessed with respect to 3 components: GI events, prescription GI medication use, and pre-

Table 1. *ICD-9-CM* Codes Selected to Define GI Events in the Pretreatment and Treatment Periods

Code	Condition	Pretreatment	Treatment
456.0	Esophageal varices with hemorrhage	X	
456.1	Esophageal varices without hemorrhage	X	
530.0x	Achalasia & caridospasm	X	
530.1x	Esophagitis	X	X
530.2	Ulcer of esophagus	X	X
530.3	Stricture of esophagus	X	X
530.4	Perforation of esophagus	X	X
530.5	Dyskinesia of esophagus	X	
530.7	Mallory-Weiss syndrome	X	X
530.81	Esophageal reflux (GERD)	X	X
530.82	Esophageal hemorrhage	X	X
530.84	Tracheoesophageal fistula	X	
530.89	Other disorders of the esophagus	X	
531.xx	Gastric ulcer	X	X
532.xx	Duodenal ulcer	X	X
533.xx	Peptic ulcer, site NOS	X	X
535.0x	Acute gastritis	X	X
535.4x	Gastritis NEC	X	X
535.5x	Gastritis/duodenitis NOS	X	X
535.6x	Duodenitis	X	X
536.2	Persistent vomiting	X	X
536.8	Dyspepsia and other specified disorders of function of stomach	X	X
536.9	Stomach function disorders NOS	X	
537.4	Gastric/duodenal fistula	X	
537.8x	Gastroduodenal disorders NEC	X	
537.9	Gastroduodenal disorders NOS	X	
578.x	GI hemorrhage	X	X
787.0x	Nausea and vomiting	X	X
787.1	Heartburn	X	X
787.2	Dysphagia	X	X
789.0x	Abdominal pain	X	X
792.1	Abnormal stool/occult blood	X	
793.4	Abnormal exam GI tract	X	

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification;* GI, gastrointestinal; GERD, gastroesophageal reflux disease; NOS, not otherwise specified; NEC, not elsewhere classified.

scription NSAID/salicylate use. In the pretreatment period, a broad list of *ICD-9* diagnosis codes was evaluated to distinguish individuals who have preexisting GI conditions and thus might be more prone to developing GI problems after initiating bisphosphonate therapy (**Table 1**). Based on the presence of preexisting GI conditions, an additional stratified analysis was conducted for the treatment period. In the 4-month treatment period, a more restricted list of *ICD-9* codes was used to define GI events, including only those conditions that could possibly be associated with bisphosphonates. GI events were examined in 2 ways: (1) those recorded as a primary diagnosis only, and (2) those recorded as a primary diagnosis and up to 4 secondary diagnoses for a particular office visit or hospitalization. GI medication use was defined as at least 1 prescription for an H_2 receptor blocker, proton pump inhibitor (PPI), and/or cytoprotective agent. NSAID/salicylate use was evaluated to assess possible differences between the alendronate and risedronate patients that could potentially influence their susceptibility to further GI irritation.

Statistical Methods. The Wilcoxon rank sum test was used to compare alendronate and risedronate patients on age, sex, number of concomitant medications (quantified by the number of therapeutic classes[30] represented by prescriptions in the pretreatment period), milligrams of oral glucocorticoids, number of hospitalizations, and number of specialist visits in the pretreatment period because the variables were continuous and not normally distributed. The chi-square test was used to compare the 2 groups receiving oral glucocorticoid (percent with at least 1 prescription). Mantel-Haenszel odds ratios (OR)[31] and 95% confidence intervals were used to compare the alendronate and risedronate patients on preexisting GI conditions, GI medication use, and NSAID/salicylate use during the pretreatment period.

For the 4-month treatment period, the 2 populations were compared on these variables using both crude and adjusted Mantel-Haenszel RR[29] estimates and 95% confidence intervals. Age, sex, and preexisting GI conditions were included in the adjusted models. Additional variables were then selected only if they significantly added to the multivariate model. Mantel-Haenszel RRs were also used to compare alendronate and risedronate

patients based on use of GI medications and NSAIDs/salicylates in the treatment period, with adjusted models including age, sex, and use of GI medications or NSAIDs/salicylates in the pretreatment period.

To provide an additional perspective, the bisphosphonate patients were also classified as having a "GI history" or "no GI history" based on the presence of 1 or more GI conditions in the pretreatment period. A stratified analysis was then carried out by using Mantel-Haenszel RRs to compare the alendronate and risedronate users and adjusting for age and sex.

Results

A total of 865 risedronate patients and 5255 alendronate patients were eligible for analysis. The mean age was approximately 76 years for both the risedronate and alendronate groups, and 93% of the patients were women, with no statistically significant differences observed (**Table 2**).

The risedronate and alendronate patients were very similar with respect to their overall health status at baseline, as indicated by the number of concomitant medications, hospitalizations, and specialist visits. No statistically significant differences were observed between the groups (Table 2). A slightly higher proportion of risedronate patients had filled a prescription for an oral glucocorticoid, but the difference was minimal and neither the percentage of patients with a glucocorticoid prescription nor the average cumulative 6-month exposure in prednisone equivalents among patients with at least 1 glucocorticoid prescription for the 2 groups (900 vs 865 mg, respectively, for risedronate and alendronate) was significantly different. Only "number of concomitant medications" was included in the final model to compare alendronate and risedronate on GI events, because it significantly contributed to the explanatory power of the model.

In the 6 months before treatment, a statistically significant higher percentage of risedronate patients (13.8%) compared with alendronate patients (11.0%) had a GI-related event (**Table 3**). Alendronate patients were 23% less likely (OR = 0.77, P = .02) to have had GI events in the pretreatment period.

Table 2. Demographics and Underlying Health Status of Patients in the 6-Month Pretreatment Period

	Alendronate n = 5255	Risedronate n = 865
Sex, n (%)		
Women	4863 (93)	802 (93)
Men	392 (7)	63 (7)
Age in years, mean (SD)	75.5 (6.6)	75.8 (6.6)
Mean number of concomitant medications	5.2	5.1
Oral glucocorticoid use (% with at least 1 prescription)	10.9	11.9
Mean mg of oral glucocorticoids*	865	900
Mean number of hospitalizations	0.17	0.14
Mean number of specialist visits	2.4	2.2

*Cumulative 6-month exposure in prednisone equivalents among patients with at least 1 glucocorticoid prescription.
SD indicates standard deviation.

Table 3. Odds of Having GI Events, NSAID/Salicylate Use, or GI Medication Use in the 6-Month Pretreatment Period

		Patients		Risk Estimates		
Treatment	Total n	n	%	OR	95% CI	*P*
GI events						
Risedronate	865	119	13.8	1.00	—	
Alendronate	5255	578	11.0	0.77	(0.63, 0.96)	.02
Prescription NSAID/salicylates						
Risedronate	865	192	22.2	1.00	—	
Alendronate	5255	1175	22.4	1.01	(0.85, 1.20)	.91
Prescription GI medications						
Risedronate	865	164	19.0	1.00	—	
Alendronate	5255	984	18.7	0.98	(0.82, 1.18)	.87

GI indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval.

The 2 groups were very similar with respect to use of potential gastric irritants; 22.2% of risedronate patients and 22.4% of alendronate patients had prescription NSAIDs or salicylates (OR = 1.01, P = .91) during the pretreatment period. Use of medications typically prescribed to treat GI problems was

Table 4. Estimated Risk of GI Events During the First 4 Months of Bisphosphonate Therapy

		Diagnosis Code in Primary Position					Diagnosis Code in Any Position				
		Patients		Risk Estimates			Patients		Risk Estimates		
Treatment	Total n	n	%	RR	95% CI	*P*	n	%	RR	95% CI	*P*
All GI events											
Risedronate	865	48	5.5	1.00	—		76	8.8	1.00	—	
Alendronate	5255	429	8.2	1.44*	(1.03, 2.00)	.03	598	11.4	1.34*	(1.04, 1.74)	.02

*Adjusted for age, sex, and previous history of GI diagnosis and number of concomitant medications in the previous period.
GI indicates gastrointestinal; RR, relative risk; CI, confidence interval.

also comparable, with 19% of the risedronate and 18.7% of the alendronate patients using prescription H_2 receptor blockers, PPIs, or cytoprotectives (OR = 0.98, *P* = .87).

Incidence of GI Events. Within the first 4 months of initiating therapy, 8.2% of the alendronate patients and 5.5% of the risedronate patients experienced a GI event based on a primary diagnosis code (**Table 4**). In the final model, adjusting for age, sex, preexisting GI conditions, and number of concomitant medications, the alendronate patients showed a 44% higher risk of GI events during the treatment period compared with risedronate patients (*P* = .03). In the analysis examining all GI events, regardless of coding in the primary position, alendronate patients had a statistically significant 34% higher risk of GI events in the first 4 months of therapy (*P* = .02).

In a stratified analysis, where patients were grouped based on their GI history, findings were similar. Among those with no history of GI events in the 6-month pretreatment period, the alendronate patients exhibited a statistically significant 49% higher risk of GI events in the first 4 months of treatment compared with the risedronate patients, adjusting for age and sex (RR = 1.49, *P* = .03). An even higher elevation in adjusted risk (57%) was observed for the patients with a known history of GI events (RR = 1.57, *P* = .05). A descriptive analysis of only esophageal events coded as the primary diagnosis revealed that 2.1% of the alendronate patients and 1.6% of the risedronate patients had an esophageal event. Given the small number of esophageal events, this difference was not statistically significant.

NSAID/Salicylate and GI Medication Use. A slightly higher percentage of alendronate (17.4%) versus risedronate (16.9%) patients had a prescription for an NSAID or salicylate during the treatment period (**Table 5**). Adjusting for previous use of these medications, the risk was comparable for the 2 groups (RR = 1.05, *P* = .71). Alendronate patients also had a somewhat higher proportion of GI medication use (18% vs 17.3%), but the adjusted RR estimate (RR = 1.02) was not statistically significant (*P* = .74).

Discussion

In the present analysis of a fully insured elderly managed care population, alendronate patients exhibited a significantly higher risk of GI events in the first 4 months of therapy compared with risedronate patients. This increased risk was observed regardless of whether the GI diagnosis was coded in the primary position or in any position. These observational results support the findings of previous head-to-head comparative endoscopy trials in that the 2 bisphosphonates did not exhibit identical profiles with respect to GI irritation. The endoscopy study by Lanza et al showed healthy, postmenopausal risedronate patients to be at significantly lower risk (4.1% incidence) for gastric ulcers compared with alendronate patients (13.2% incidence).[20] Similarly,

Thomson et al demonstrated more potential for gastric irritation by alendronate than risedronate, with rates of gastric ulcer found to be 12.1% and 6%, respectively.[21]

These results also offer a unique perspective of clinical practice that cannot be explored via randomized clinical trials or endoscopic studies. For example, patients with preexisting GI problems were excluded from the alendronate clinical trials and treated patients appeared to have a GI event rate similar to placebo.[3-5] Once alendronate was available on the market, however, real-world use of the drug was associated with an increased number of esophagitis and esophageal strictures.[2] Observational database studies have several advantages over controlled clinical trials in that real-world practice patterns can be observed over a variety of health plans and physician specialties, a large number of patients can be followed over time, and the patients may be more typical of those seen in actual practice, because they are not excluded by restrictive clinical trial exclusion criteria. Additionally, it is possible to generate comparative data for conditions with relatively low incidence because a sizable patient population can be readily evaluated.

There are several limitations of administrative claims database research as well. Patient charts cannot be reviewed to confirm the accuracy of diagnosis codes, unknown variables (such as compliance with pill-taking instructions or others not captured in a database) could influence treatment and outcomes, and only clinically reported events can be evaluated. Specifically, with respect to the evaluation of GI events, only those conditions severe enough to warrant medical service (eg, physician visit) and subsequently receive an *ICD-9* diagnosis code are counted. If the patient merely mentions the GI complaint as a secondary concern, then it is less likely to be coded. Another limitation is the accuracy of the specific *ICD-9* codes assigned to the patient. The individual responsible for coding the patient's visit might select one *ICD-9* code over another because of reimbursement associated with a specific code. Additionally, a physician's preconceptions about a particular therapy can potentially lead to over- or underdiagnosis of a certain condition among those treated patients.

Table 5. GI Medication and NSAID/Salicylate Use in the First 4 Months of Therapy (Treatment Period)

		Patients		Risk Estimates		
Treatment	**Total n**	**n**	**%**	**RR**	**95% CI**	***P***
GI medication use						
Risedronate	865	146	16.9	1.00	—	
Alendronate	5255	915	17.4	1.05*	(0.93, 1.20)	.71
NSAID/salicylate use						
Risedronate	865	150	17.3	1.00	—	
Alendronate	5255	946	18.0	1.02†	(0.89, 1.17)	.74

*Adjusted for age, sex, and previous history of GI medications.
†Adjusted for age, sex, and previous history of NSAIDs/salicylates.
GI indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; CI, confidence interval.

Patients included in this analysis are representative of a fully insured elderly population, which is eligible to receive prescriptions for osteoporosis therapy in a managed care setting. This study did not explore bisphosphonate use among patients who lack health insurance (medical and/or prescription) benefits or the differences in patterns of care among patients with differing copayment structures because the data were not available.

While the primary focus of this analysis was to evaluate differences in the incidence of GI events (via *ICD-9* codes), use of medications to treat such GI events was also assessed. Most GI events are treated with PPIs, H_2 receptor blockers, or cytoprotectives. Because many forms of these therapies are available over the counter, it is difficult to truly assess their use in an administrative claims database that captures only prescription products. Furthermore, any medications that were dispensed in a hospital setting are rolled into a single claim for the hospital visit and cannot be identified individually. Thus, in the present study, use of GI medications is likely to be underreported for both bisphosphonates. Whether or not there is differential underreporting is unknown.

In observational database analyses, it is also of interest to establish the comparability

of patient populations at baseline or before treatment. For the present study, it was important to understand whether the treatment groups were similar in their underlying risk for incurring a GI problem. For the 6-month pretreatment period, we considered patients to have a GI history if they had at least 1 *ICD-9* code for a GI-related condition. This served as a surrogate for chart review (which typically is not available in a claims database) and for more definitive yet invasive evaluations, such as endoscopy. As seen in Table 3, risedronate patients were notably more likely to have had a GI condition before initiating therapy. This was accounted for in the analysis, however, via both statistical adjustment and stratification based on GI history. Other more general measures of health status were also considered, including concomitant medication use, number of specialist visits, and hospitalizations. In this study, treatment group comparability does not appear to be an issue affecting study results. The risedronate and alendronate groups showed no significant differences with respect to these health status indicators, lending support to the assumption that the 2 populations were fairly comparable overall.

Another issue that arises in database research is the appropriate classification of patients who switch therapies during the follow-up period. In the present study, we excluded any patient who switched products during the 4-month treatment period. This eliminates the potential for confusion in assignment of GI events to the current versus before therapy. Noteworthy is that by excluding these patients it was not possible to examine those who switched therapies, potentially as a result of a GI event. Evaluating switching patterns is important in understanding tolerability with therapies used in a naturalistic setting, as seen in a study by Hamilton et al, to determine compliance with risedronate dosing instructions.[32] The authors concluded that one third of patients who discontinued risedronate therapy because of adverse events began therapy again. Of those who did resume therapy, adverse events subsided in half of the patients, and they were able to continue their full course of therapy. In the present study, less than 5% of the potential sample was eliminated on the basis of a product switch during follow-up.

Conclusion

In summary, the present study showed that within the first 4 months of treatment, patients taking alendronate had a significantly higher risk of incurring a GI event compared with patients taking risedronate. No difference in GI tolerability was observed between the weekly and daily doses of alendronate. Additionally, patients with preexisting GI problems were significantly more likely to initiate therapy with risedronate than alendronate. Tolerability issues, including differences in the incidence of GI-related events, have important implications not only for the patient, but also the managed care organization and clinical pharmacist. Opportunities exist in a managed care setting to improve utilization management as well as reduce the risk of GI events in patients receiving bisphosphonate therapy. To ensure treatment effectiveness, physicians must be deliberate in providing accurate instructions to the patient on administration techniques and carefully monitor patient adherence to treatment regimens. In turn, the patient must fully understand the implications of nonadherence to these instructions to reduce the likelihood of GI events. Utilization management strategies must direct appropriate prescribing to patients without a documented history of at-risk conditions to prevent future GI events as well. Excess events may lead to a substantial increase in healthcare costs (ie, medications, hospitalizations, physician visits) for patients receiving a particular therapy. Additional research, including an economic analysis of the medical costs and resource utilization associated with each therapy, can further illustrate the importance of such tolerability differences and quantify the impact for managed care.

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