HORMONES 2007, 6(3):233-241

Research paper

Oral bisphosphonate adverse effects in 849 patients with metabolic bone diseases

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ABSTRACT

OBJECTIVE: Bisphosphonates are potent antiresorptive agents used for a spectrum of metabolic bone diseases. The aim of this study was to compare the adverse effects (AEs) of alendronate, etidronate and risedronate prescribed in a non-selected population, attending a single institution on an outpatient basis. DESIGN: 849 patients receiving either alendronate (n=710), etidronate (n=181) or risedronate (n=130) were studied for a period of 1916 person-years. RESULTS: AEs were reported by 25.2% [21% gastro-intestinal (GI) system-related], 11.1% (9.9%) and 20.8% (15.4%) of patients on alendronate/etidronate/risedronate, respectively, resulting in permanent discontinuation in 21.0%, 7.7% and 13.8%, respectively. The odds ratio (95% CI) for AEs in the case of a history of GI disease was 2.4 (1.4-3.8), 2.1 (0.8-5.1) and 2.5 (0.9-6.6), respectively. The majority of AEs were of a mild nature and usually occurred within six months of therapy initiation. The odds ratio for AEs given the concurrent use of NSAIDs was 2.0 (1.4-3.0), 0.8 (0.3-2.4) and 2.2 (0.8-5.9), respectively. CONCLUSIONS:. Etidronate appears to have a better AE profile. Bisphosphonate AEs are fairly mild, affect the GI system, occur most frequently in the presence of GI disease or concurrent use of NSAIDs and tend to be of the same type in the event of administration of a different bisphosphonate.

Key words: Adverse effects, Alendronate, Bisphosphonates, Etidronate, Osteoporosis, Risedronate

INTRODUCTION

Postmenopausal osteoporosis is a major public health problem. Bisphosphonates are potent antiresorptive agents, which can be used for both osteoporosis prevention and treatment[1] and have proved their efficacy in a wide spectrum of metabolic bone diseases, including Paget's disease, osteogenesis imperfecta and primary hyperparathyroidism. As a consequence, a great number of physicians of many specialties need to be familiar with the adverse effects (AEs) profile of these agents.

The vast majority of studies dealing with AEs of bisphosphonates focus only on their impact on the upper gastrointestinal (GI) system, while fewer studies refer to AEs from other systems.

The studies dealing with upper GI system AEs in

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Received 15-02-07, Revised 10-04-07, Accepted 15-06-07

patients receiving bisphosphonates can be divided into those with endoscopic confirmation of their findings[2-6] and those without endoscopic confirmation.[7-9] The endoscopic studies have better methodology but carry the disadvantages of smaller sample size and shorter period of follow-up, usually one to four weeks. Non-endoscopic studies have more methodological problems but are of longer duration: up to ten years with alendronate,[10] seven years with etidronate[8] and seven years with risedronate.[11] The results of endoscopic and non-endoscopic studies are conflicting with regard to prevalence and location of AEs.

Most of the studies evaluated the AEs of only one bisphosphonate,[9,12-14] while some directly compare two of them, usually alendronate and risedronate.[3,6,15,16] To our knowledge, no previous study exists which directly compares all bisphosphonates commercially available.

Finally, the majority of the studies dealing with bisphosphonates AEs do not reflect everyday clinical practice, as they report on clinical trials which are designed to answer specific questions and have a great number of inclusion and exclusion criteria.

The aim of the present study was to record and compare the complete AE profile of all three bisphosphonates currently available on the Greek market, namely alendronate, etidronate and risedronate, prescribed in a non-selected population attending a single tertiary care institution on an outpatient basis and followed up by the same team of physicians.

PATIENTS AND METHODS

Patients

The study included 849 patients with metabolic bone disease [48 men/801 women, age (mean ± standard deviation) 61.8 ± 9.9 years] who received at least one type of oral bisphosphonate between January 1996 and June 2004 for an overall period of 1916 person-years. All of them were attending the outpatient clinics of the Department of Endocrinology, Hippocration General Hospital, Thessaloniki, Greece, a tertiary referral center for metabolic bone diseases. All patients who received bisphosphonates during that period were included, irrespective of their sex or disease for which bisphosphonates were prescribed. Metabolic bone diseases included postmenopausal osteoporosis (n=727), glucocorticoid-induced osteoporosis (n=66), male osteoporosis (n=19), Paget's disease (n=16), juvenile osteoporosis (n=4), hyperparathyroidism (n=14) and osteogenesis imperfecta (n=3). Baseline characteristics of the patients are given in Table 1.

Methods

Before drug administration, a detailed medical

Table 1. Patients' characteristics.

	All patients N(%)	Alendronate N(%)	Etidronate N(%)	Risedronate N(%)
	849	710	181	130
Age (years)	61.8 ± 9.9	61.8 ± 10.1	62.1 ± 9.6	61.4 ± 9.0
Gender (female)	801 (94.3)	665 (93.7)	174 (96.1)	126 (96.9)
Postmenopausal osteoporosis	727 (85.6)	601 (84.6)	161 (89.0)	118 (90.8)
Co-morbidity				
history of malignancy	33 (3.9)	27 (3.8)	7 (3.9)	17 (13.1)[a,b]
history of GI system disease	136 (16.0)	95 (13.4)	54 (29.8)[a]	30 (23.%)[a]
Concurrent therapy				
glucocorticoids per os	60 (7.1)	52 (7.3)	9 (5.0)	12 (9.2)
NSAIDs	328 (38.6)	288 (40.6)	81 (44.8)	48 (36.9)
aspirin	73 (8.6)	56 (7.9)	13 (7.2)	16 (12.3)
Treatment duration (months) mean±SD	27.1 ± 19.9	25.8 ± 19.3	17.2 ± 12.0	12.0 ± 6.6

GI: gastro-intestinal, NSAIDs: non-steroidal anti-inflammatory drugs. Data are presented as absolute values (percentage) or mean ± standard deviation. [a] $p<0.05$ vs. alendronate, [b] $p<0.05$ vs. etidronate (Mantel-Haenszel).

history was taken and a basic biochemical profile was performed that included complete blood count, urea, creatinine, total serum protein, serum albumin, liver enzymes, serum calcium, serum phosphate and alkaline phosphatase. Additional investigation that included thyroid-stimulating hormone (TSH), free thyroxine (FT_4), parathyroid hormone (PTH) and 24-hour urine for calcium was performed whenever clinical suspicion was raised in order to diagnose secondary forms of osteoporosis. Patients were instructed on the proper way of receiving bisphosphonates (on an empty stomach, with a full glass of water and avoidance of food or lying down for half an hour).

Bisphosphonate dosage was kept uniform, specifically 10 mg daily for alendronate, 400 mg daily for 15 days every three months for etidronate and 5 mg daily for risedronate. An important exception was patients with Paget's disease who were receiving etidronate at a dosage of 400 mg daily. The criteria used to prescribe a specific bisphosphonate included: 1) availability: chronological order of appearance on the Greek market, 2) AE profile: risk for AEs, given the patient's personal history, 3) efficacy: reported efficacy in the literature/observed efficacy in the patient. All of the patients were receiving 500 - 1000 mg of elemental calcium and 400 - 800 IU of vitamin D daily.

Patients were followed up at the outpatient clinic at intervals of three to twelve months according to the severity of their disease. As a routine procedure, at every visit patients were specifically asked if they had experienced any AEs since the last visit; nevertheless, there was no specific referral to the nature of AEs that could have been experienced. Unscheduled visits were arranged by the patients in the event of serious changes in the clinical condition. Recording of all data was made using the on-line electronic patient database developed by and used by the Department of Endocrinology, Hippocration General Hospital, Thessaloniki, Greece.

The association of a reported AEs with bisphosphonate use was made mainly on clinical grounds. In most of the cases, especially in patients with mild epigastric pain, further confirmation was sought using a discontinuation - re-initiation procedure. In cases of severe upper GI system symptoms, patients were referred, whenever possible, for endoscopic evaluation in order to confirm the damage and estimate the nature and exact location of it. Due to its intermittent use, etidronate AEs were evaluated during the therapy period.

Statistics

Data are described as mean ± standard deviation (SD) for continuous variables or as absolute numbers (percentage) for categorical variables. A p value of less than 0.05 was considered as statistically significant. The Mantel-Haenszel method was used in order to test for differences between groups in dichotomous variables. Study variable correlation was made by means of Pearson's correlation test. A stepwise discriminant analysis was performed using the Wilks' Lambda statistic in order to weigh the addition or removal of variables from the procedure. Odds ratios and 95% confidence intervals (CI) were calculated using Gart's method. The statistical analysis was performed using SPSS for Windows, version 13, SPSS Inc, Ill, USA.

RESULTS

Patient characteristics and data on bisphosphonate use are presented in Table 1. The 849 patients included in the study took at least one bisphosphonate: alendronate (n=710), etidronate (n=181) or risedronate (n=130). The total number of AEs reported referred to greater than 849, as some patients used more than one bisphosphonate at different time periods. There were no statistically significant differences among groups regarding age, sex, indication for bisphosphonate prescription or concurrent medications. On the other hand, the patients on risedronate had a statistically significant greater prevalence of malignancies in their medical history, whereas the patients on alendronate had a lower prevalence of history of GI system disease as compared to the other groups (Table 1).

Prevalence of AEs is presented in Table 2. The patients on alendronate had the higher AE prevalence, followed by those on risedronate and etidronate. The same pattern was recorded regarding permanent drug discontinuation related to AEs. The most common AEs for all treatment groups were related to the upper GI system. Although the etidronate-treated patients had a higher prevalence of history of GI system disease, the prevalence of AEs in this group was the lowest, followed by the risedronate and al-

Table 2. Prevalence of adverse effects.

	Alendronate N(%)	Etidronate N(%)	Risedronate N(%)
Patients treated	710	181	130
Adverse effects	179 (25.2)[b]	20 (11.1)	27 (20.8)[b]
permanent drug discontinuation (percentage of patients that used bisphosphonates)	149 (21.0)[b]	14 (7.7)	18 (13.8)
permanent drug discontinuation (percentage of patients that experienced AEs)	149 (83.2)	14 (70.0)	18 (66.7)
GI system AEs	149 (21.0)[b]	18 (9.9)	20 (15.4)
upper GI system AEs	134 (18.9)[b]	16 (8.8)	17 (13.1)
lower GI system AEs	15 (2.1)	2 (1.1)	3 (2.3)
Non-GI system AEs	30 (4.2)	2 (1.1)	7 (5.4)
History of GI system disease	95 (13.4)	54 (29.8)[a]	30 (23.1)[a]
AEs in patients with history of GI system disease	42 (44.2)[b]	11 (20.4)	12 (40.0)

AEs: adverse effects, GI: gastro-intestinal. Data are presented as absolute values (percentage). [a] $p<0.05$ vs. alendronate, [b] $p<0.05$ vs. etidronate (Mantel-Haenszel).

endronate groups.

The types of AEs are presented in Table 3. Rare AEs in the alendronate group were somnolence lasting a few hours after taking the pill (n=2), anterior uveitis (n=1), pharyngeal dryness (n=1), bitter taste lasting a few hours after taking the pill (n=1), lower limb numbness (n=1) and lower limb edema (n=1). Rare AEs in the etidronate group were rash/pruritus (n=1) and pain in the flank (n=1). Finally, rare AEs in the risedronate group were rash/pruritus (n=1), bone pain/arthralgia (n=2), myalgia (n=1), erythema nodosum (n=1) and glossitis/pharyngeal dryness (n=1).

Time of AEs onset is presented in Table 4. The majority of AEs usually occurred within six months after bisphosphonate initiation. In the case of a late-onset (after 6 months) the AE were almost exclusively related to the GI system. Specifically, out of 77 alendronate-treated patients who experienced a late-onset AE, only three cases were not related to the GI system: two patients with rash/pruritus and one patient with bone pain/arthralgia. In all six etidronate-treated patients with a late-onset AE, this was related to the GI system. Finally, in three out of four risedronate-treated patients with a late-onset AE, this was related to the GI system, whereas the fourth patient complained of bone pain.

An analysis of the subgroup of patients that experienced GI system AEs is presented in Table 5. Six patients in the alendronate group had esophagitis confirmed by upper GI tract endoscopy. The odds ratio (95% CI) for an AE given a personal history of GI system disease was 2.4 (1.4-3.8) for alendro-

Table 3. Type of adverse effects.

	Alendronate N (%)	Etidronate N (%)	Risedronate N (%)
Numbers of patients treated	710	181	130
Patients with AEs	179	20	27
GI system AEs	149 (83.3)	18 (90.0)	20 (74.1)
upper GI system AEs	134 (74.9)	16 (80.0)	17 (63.0)
lower GI system AEs	15 (8.4)	2 (10.0)	3 (11.1)
Non-GI system AEs	30 (16.8)	2 (10.0)	7 (25.9)
allergic reaction	7 (3.9)	1 (5.0)	1 (3.7)
bone pain	8 (4.5)	0 (0.0)	2 (7.4)
arthralgia	7 (3.9)	0 (0.0)	1 (3.7)
myalgia	1 (0.6)	0 (0.0)	1 (3.7)
other	7 (3.9)	1 (5.0)	2 (7.4)

AEs: adverse effects, GI: gastro-intestinal. Data are presented as absolute values (percentage).

Table 4. Time of adverse effect presentation.

	Alendronate N(%)	Etidronate N(%)	Risedronate N(%)
Patients treated	710	181	130
Patients with AEs	179 (25.2)[b]	20 (11.1)	27 (20.8)[b]
Duration of drug administration months (range)	6-78	6-54	6-24
Onset of AEs post initiation			
within first week	38 (21.2)[b]	12 (60.0)	10 (37.0)
within first month	69 (38.5)	14 (70.0)[a]	17 (63.0)[a]
2-6 months	102 (57.0)	0 (0.0)	23 (85.2)
during the 1st year	125 (69.8)	0 (0.0)	0 (0.0)
at the end of the 1st year	16 (8.9)	4 (20.0)	3 (11.1)
during the 2nd year	28 (15.6)	2 (10.0)	1 (3.7)
during the 3rd year	7 (3.9)	-	-
during the 4th year	2 (1.1)	-	-
during the 5th year	1 (0.6)	-	-

AEs: adverse effects, GI: gastro-intestinal. Data are presented as absolute values (percentage). [a] $p<0.05$ vs. alendronate, [b] $p<0.05$ vs. etidronate (Mantel-Haenszel).

nate, 2.1 (0.8-5.1) for etidronate and 2.5 (0.9-6.6) for risedronate.

Some patients experienced AEs in more than one biphosphonate. In the majority of the cases, the same AEs were recorded, irrespective of the agent used. Specifically, out of 21 alendronate-treated patients that experienced AEs, not only with alendronate but with another agent as well, the AEs were the same in 16 cases and different in the remaining five cases. Corresponding recordings were: six cases with the same AEs and three with different AEs for etidronate and ten cases with the same AEs and two with different AE for risedronate. Finally, one patient, who had AE with all three bisphosphonates, experienced the same AE (esophagitis) with all agents.

If a patient had experienced an AE with a bisphosphonate and a decision was made to change to another one, he/she had once again an AE at a rate of 70.0% if the second agent was alendronate, 37.5% if it was risedronate but only 16.4% if it was etidronate.

Table 5. Adverse effects from the gastro-intestinal system.

	Alendronate N(%)	Etidronate N(%)	Risedronate N(%)
Patients with AEs	179 (25.2)	20 (11.1)	27 (20.8)
GI system AEs	149	18	20
Upper GI system AEs	134 (74.9)	16 (80.0)	17 (63.0)
esophageal disease: gastroesophageal reflux, esophagitis	44 (32.8)	5 (31.3)	7 (41.2)
gastric disease: gastritis, ulcer, epigastric pain	81 (60.5)	11 (68.7)	8 (47.1)
non-specific GI disease: nausea, vomiting	8 (6.0)	0 (0.0)	2 (11.7)
upper GI hemorrhage	1 (1.0)	0 (0.0)	0 (0.0)
Lower GI system AEs	15 (8.4)	2 (10.0)	3 (11.1)
flatulence, abdominal pain	7 (46.6)	0 (0.0)	2 (66.7)
constipation	4 (26.7)	1 (50.0)	0 (0.0)
diarrhea	4 (26.7)	0 (0.0)	1 (33.3)
ulcerative colitis	0 (0.0)	1 (50.0)	0 (0.0)

AEs: adverse effects, GI: gastro-intestinal. Data are presented as absolute values (percentage).

The analysis of the AEs in patients receiving concurrent medication is presented in Table 6. We specifically investigated the concurrent use of oral and inhaled glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. There was no statistically significant increase of the prevalence of AEs in patients taking glucocorticoids or aspirin in any of the three treatment groups. On the other hand, patients that used NSAIDs had higher prevalence of any type of AE. The odds ratio (95% CI) for an AE given the use of NSAIDs was 2.0 (1.4-3.0) for alendronate, 0.8 (0.3-2.4) for etidronate and 2.2 (0.8-5.9) for risedronate-treated patients.

A stepwise discriminant analysis (multiple regression) was performed with the presence of AEs as the dependent variable and age, sex, indication for bisphosphonate prescription, diagnosis of osteo-

Table 6. Adverse effects in patients receiving concurrent medication.

	Alendronate N(%)	Etidronate N(%)	Risedronate N(%)
Number of patients treated	710	181	130
Concurrent therapy			
glucocorticoids			
per os	52 (7.3)	9 (5.0)	12 (9.2)
inhaled	30 (4.2)	7 (3.8)	9 (6.9)
none	628 (88.5)	165 (91.2)	109 (83.9)
NSAIDs			
yes	288 (40.6)	81 (44.8)	48 (36.9)
no	422 (59.4)	100 (55.2)	82 (63.1)
aspirin			
yes	56 (7.9)	13 (7.2)	16 (12.3)
no	654 (92.1)	168 (92.8)	114 (87.7)
AEs	179	20	27
glucocorticoids			
per os	13 (7.3)	2 (10.0)	1 (3.7)
inhaled	12 (6.7)	1 (5.0)	5 (18.5)
none	154 (86.0)	17 (85.0)	21 (77.8)
NSAIDs			
yes	96 (53.6)	8 (40.0)	14 (51.9)
no	83 (46.4)	12 (60.0)	13 (48.1)
aspirin			
yes	17 (9.5)	1 (5.0)	5 (18.5)
no	162 (90.5)	19 (95.0)	22 (81.5)

AEs: adverse effects, GI: gastro-intestinal, NSAIDs: non-steroidal anti-inflammatory drugs. Data are presented as absolute values (percentage).

arthritis, diagnosis of concomitant diseases, use of aspirin/glucocorticoids/NSAIDs and history of GI system disease as independent variables. The four parameters that remained in the analysis were history of GI system disease, use of NSAIDs, indication for bisphosphonate prescription and diagnosis of concomitant diseases. These discriminanting variables used together were able to correctly predict the presence of an AE in 63.5% of the cases.

DISCUSSION

A non-selected population of 849 patients with metabolic bone diseases treated with oral bisphosphonates on an outpatient basis over a period of 1916 person-years were studied in an attempt to record and compare the complete AEs profile while on either alendronate, etidronate or risedronate treatment.

This study had all the disadvantages of a retrospective trial: it was not specifically designed to compare AEs of bisphosphonates and the patients were not randomly assigned to the three treatment groups. On the other hand, the study reflects everyday clinical practice as it includes non-selected patients in need of treatment with bisphosphonates and followed over a long period of time in the same center.

The three treatment groups were comparable in age, sex and indication for bisphosphonate prescription. There was no apparent explanation for the higher prevalence of malignancy in the past or in the family history of the risedronate group; this was probably a random effect. Patients of the etidronate group had higher prevalence of history of GI system disease; this was a result of the prescription attitude, as since 1997 there has been evidence that etidronate has a mild AE profile.[8] There were no differences among groups in concurrent medications. Patients on alendronate were receiving bisphosphonates for longer periods of time; this probably stemmed from two causes: longer availability of alendronate as compared to risedronate and transition of patients from etidronate to alendronate, as there was accumulated evidence that the latter was more efficacious than the former in terms of bone mineral density improvement.

The main finding in our study was that the prevalence of AEs was lower in the etidronate group followed by risedronate and alendronate. We consider this as probably true difference. Although the patients in the various treatment groups were not randomly distributed, the main epidemiologic characteristics were comparable. In addition, the etidronate-treated patients had a higher percentage of NSAID use, a parameter that could increase the AE rate. An explanation for the difference detected could be the intermittent way of etidronate administration. This speculation is further supported by the excellent AE profile, similar to that of placebo, of the once weekly formulas of alendronate 70 mg and risedronate 35 mg.[6,17]

Our findings are in agreement with those of other studies reporting no increased risk of GI system AEs with cyclical etidronate[8,9,18] and no significant difference in the AE rate between risedronate and etidronate.[3,13,19,20]

As also reported by other studies,[7,21,22] we found

that the most frequent AEs for bisphosphonates were abdominal pain, nausea/vomiting, dyspepsia, esophagitis and esophageal reflux. Alendronate can irritate the esophagus either by toxicity from the medication itself or, more likely, by non-specific insult secondary to contact of the pill and the esophageal mucosa, similar to other cases of "pill esophagitis".[2] Although an upper GI system endoscopy was not performed in a systematic way, we were able to detect cases of chemical esophagitis, with erosions or ulcerations in patients who underwent endoscopy. In the literature, conflicting results have been reported in endoscopic studies, as some reported no increase[4] and others a higher prevalence of gastric, but not esophageal, lesions among patients taking oral bisphosphonates.[5] Randomized, controlled trials, suggested little or no increase in risk of upper GI tract AEs, if bisphosphonates are administered properly.[1] Besides, upper GI system symptoms are common among osteoporotic patients, suggesting that many upper GI tract AEs reported during therapy with bisphosphonates may reflect a high background prevalence of upper GI system complaints and an increased sensitivity of detection rather than a causal relationship to therapy.[23]

The odds ratio for an AE in our study was more than double in the case of a GI system disease in a patient's history. It is generally considered that bisphosphonates with a primary amine, such as alendronate, are more irritating to the GI tract than those without a primary amine, such as etidronate.[24] Risedronate has been associated with a significantly lower prevalence of gastric ulcers than alendronate.[6,25] However, Peter et al reported no greater gastric irritation potential for alendronate in comparison to etidronate or risedronate in a rat model.[26]

Due to the magnitude of the study and, especially, the lack of specific inclusion and exclusion criteria, we were able to detect rare AEs, such as somnolence, uveitis and erythema nodosum. The prevalence of any one of them ranged from 0.1% to 0.2%. In our series we had only mild cases of oral and pharyngeal manifestations, such as pharyngeal dryness, bitter taste and glossitis. There are reports of severe oral ulcerations due to sucking alendronate tablets instead of swallowing them.[27] This misuse of alendronate underlines the risk of direct mucosal injury with this drug.[28] We have detected a case of anterior uveitis in an alendronate-treated patient. Uveitis has been linked to both alendronate[29] and risedronate.[30,31] The ocular manifestations occur rapidly after treatment introduction and resolve on treatment cessation.[32] Etidronate seems to be exempt from this ocular risk.[33] In contrast, in our series we had no cases of facial edema,[22] angioedema, erythema multiforme, severe hypercalcemia or hypocalcemia,[7] pancreatitis,[34] toxicoderma,[35] urticaria,[36] lichen planus,[37] seizures,[38] acute renal failure[39] or hepatocellular damage encountered in other studies.[40-43] Damage of the liver is a quite rare complication, which has been reported solely after alendronate usage and it resolves rapidly after therapy discontinuation. We also had no cases of ototoxicity, a rare and disabling complication reported in etidronate-treated patients,[44] or osteonecrosis of the jaw.[45] We also had no evidence of "frozen bone" with long-term use of any bisphosphonate.[46,47]

In our group the majority of AEs were mild and of early-onset, defined as an AE within six months after bisphosphonate initiation. In particular, 70% of AEs in the etidronate group were apparent within the first month of therapy. To our knowledge, there are no studies in the literature that have approached the issue of bisphosphonate AEs in a time-oriented way.

The use of NSAIDs increased the prevalence of any type of AE in the alendronate and risedronate but not in the etidronate treated patients. In accord with our study, a synergistic ulcerogenic potential and an increased risk of upper GI system AEs with concurrent alendronate or risedronate and NSAIDs use,[20,48,49] but not with concurrent cyclical etidronate and NSAIDs, aspirin or corticosteroids use,[18] have been reported. Other studies reported no increase in upper GI system AEs in concurrent NSAIDs use with alendronate[12] or risedronate.[14,50]

Whenever a patient was intolerant to a certain bisphosphonate, a change to a different bisphosphonate was made. Etidronate was once again proved to have a better AE profile. Few studies have dealt with AEs in patients who used sequentially more than one bisphosphonate. Adachi et al found a risedronate GI tolerability similar to that of the placebo in postmenopausal women who had discontinued alendronate treatment because of upper GI system AEs.[51] In our patients, the sequential use of a second bisphosphonate was associated with the same AE. This may indicate a predisposition for specific AEs in some individuals, which remains unchanged throughout all agents in

the bisphosphonate class.

In conclusion, we have conducted a study in order to record and compare complete AE profile of oral bisphosphonates. The main findings were that etidronate had a better AE profile as compared to alendronate or risedronate in at least three aspects: overall AE rate, AE rate when used concurrently with NSAIDs and when used to substitute for another bisphosphonate agent, after experience of an AE with the previous one. The final decision for prescribing a particular bisphosphonate was not only the result of its AE profile but its efficacy as well, an area where alendronate or risedronate are superior, especially regarding the non-vertebral fractures.[52] Additional findings of the study were that, in general, bisphosphonate AEs affecting the GI system were usually mild, were of early onset, increased in the case of a previous history of GI disease or concurrent use of NSAIDs and tended to be of the same type in the event of administration of another bisphosphonate. The four parameters that can better predict the presence of an AE were history of GI system disease, use of NSAIDs, indication for bisphosphonate prescription and diagnosis of concomitant diseases. The present data have to be viewed in concordance with randomized controlled trials or post-marketing surveillance of similar content.

ACKNOWLEDGMENT

We thank Prof. George Kitas, Professor of Rheumatology, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK, for his valuable comments throughout the preparation of this manuscript.

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