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ORIGINAL ARTICLE

Prodromal Symptoms in Patients with Bisphosphonate-Associated Atypical Fractures of the Femur

Mohammad Kharazmi · Karl Michaëlsson · Pär Hallberg

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Abstract Symptoms have been reported to precede bisphosphonate-associated atypical fractures (AFs) of the femoral shaft. We aimed to determine the frequency and clinical characteristics of such prodromal symptoms. We searched the Swedish national database of spontaneously reported adverse drug reactions for all cases of AF associated with bisphosphonates from January 2006 to March 2013. To confirm diagnostic accuracy and to characterize and determine the frequency of any prodromal symptoms we retrieved copies of medical journals and radiographs for patients who consented to participate in the study. The frequency of prodromal symptoms was compared with that of patients where information was based only on narratives from the adverse drug reaction case reports. A total of 45 reports of AF were identified. We were able to obtain medical records and x-rays for 21 cases and diagnostic accuracy was confirmed for all. Medical records revealed prodromal symptoms in 86 % ($n = 18$), most commonly pain in the ipsilateral thigh (14 out of 18 patients) preceding the fracture for weeks or longer. Awareness of such symptoms may facilitate early diagnosis and possible prevention of the AF.

M. Kharazmi (✉)
Department of Oral and Maxillofacial Surgery, Central Hospital, Västerås, 721 89 Västerås, Sweden
e-mail: kharazmi.mohammad@gmail.com

M. Kharazmi · K. Michaëlsson
Section of Orthopaedics, Department of Surgical Sciences, Uppsala University, 751 85 Uppsala, Sweden
e-mail: karl.michaelsson@surgsci.uu.se

P. Hallberg
Department of Medical Sciences, Uppsala University, 751 85 Uppsala, Sweden
e-mail: par.hallberg@medsci.uu.se

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Introduction

Since the mid-1990s bone anti-resorptive therapy with bisphosphonates has been the gold standard for fracture reduction in patients with osteoporosis. However, concerns have also been raised about conceivable over-suppression of bone turnover during long-term use leading to impaired mechanical properties of the bone. Beginning in 2005 [1] an increasing number of bisphosphonate-related cases of femoral shaft fractures with an atypical appearance have been reported. After some years of uncertainty [2] there is now, based on epidemiologic evidence, a strong established association between bisphosphonate use and AFs of the femoral shaft [3, 4]. These fractures heal slowly and their impact on morbidity and quality of life is substantial [5].

As with all adverse drug reactions (ADRs) prevention remains the optimal goal. In this respect prodromal symptoms can be used to identify individuals at risk and for appropriate management, aiming to possibly avoid or minimize the risk of full manifestation of an AF.

Several publications on bisphosphonate-associated AFs have described prodromal symptoms, most commonly pain in the ipsilateral thigh. In these studies, however, investigation of prodromal symptoms was not the primary objective and such symptoms were only reported if encountered. In the present study we aimed to characterise these symptoms and to determine their frequency in patients with bisphosphonate-associated AFs reported to the Swedish Medical Products Agency (MPA) as suspected ADRs. Moreover, based on the available knowledge we

propose a management schedule for patients undergoing bisphosphonate therapy presenting with these symptoms.

Materials and Methods

The basis of the current study was the Swedish national database of spontaneously reported ADRs (Swedish Drug Information System, SWEDIS). This database contains reports sent by Swedish physicians to the Swedish Medical Products Agency (MPA) since 1965. As of May 31, 2013 there were a total of ~120,000 reports in the database. In SWEDIS a Swedish dictionary is used for coding ADRs built in a three-level hierarchical structure developed by the MPA. The first level is the system organ class, followed by group terms, and finally preferred terms. The dictionary holds a little over 1,000 preferred terms. The information in a report consists of patient demographics, reported ADRs, medication and a case narrative often accompanied by copies of medical records. All reports are reviewed by clinical assessors at the MPA and a causality assessment is made; i.e., drugs are adjudicated either as suspected causative agents or as concomitant drugs unrelated to the ADR. All drugs are coded using the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology International Anatomical Therapeutic Chemical (ATC) classification.

We searched SWEDIS for all patients who had been reported from January 1, 2006 through March 31, 2013 as having experienced AFs associated with bisphosphonates. As SWEDIS does not include a specific term for this ADR we retrieved and reviewed all reports under the group term "skeletal disorders" where a bisphosphonate was the suspected causative agent and the MPA had assessed causality as being at least possible. We limited inclusion to reports of an AF where the indication for bisphosphonate therapy was osteoporosis or its prevention.

As part of the SWEDEGENE project, a Swedish nationwide research project aiming to identify genetic causes of ADRs, we asked living patients who had been reported to experience AF to consent to accessing of their medical records and x-rays (Ethics Approval 2010/231, Uppsala, Sweden). X-rays were analysed to verify diagnostic accuracy [3]. Only those with a positive confirmation of the diagnosis were to be finally included in the present study. Medical records of the included cases were then reviewed for documentation of possible prodromal symptoms. These were not only limited to the patients' orthopaedic records.

Results

A total of 52 reports of AF were identified in SWEDIS during the time period studied. All had been coded with the preferred term "fracture pathological". Forty-five reports fulfilled the criteria for the study and seven were excluded due to a treatment indication other than osteoporosis.

Table 1 Patient demographics, duration of drug use and frequencies of prodromal symptoms-groups A and B

	Verified group A	Unverified group B
Number of reports	21	24
Gender (male/female)	2/19	0/24
Mean age (years, with range)	71.0 (58–83)	74.5 (49–89)
Mean duration of drug use (years)	6.0 ($n = 19$)	6.5 ($n = 17$)
Number of cases with prodromal symptoms based on case narratives	10	11
Number of cases with prodromal symptoms based on case narratives and medical records	18	N/A

We were able to obtain consent to retrieve medical records and digitized radiographs for 21 out of the 45 cases (Table 1). All fractures had a typical appearance of AF [3], hence diagnostic accuracy was confirmed for all 21 cases (designated group A, Table 2). This left 24 unverified cases (designated group B, Table 3) for whom only clinical information from the ADR case report narrative was available. Characteristics for the two groups are presented in Table 1, 2 and 3.

In group A the patients' age ranged from 58 to 83 (mean 71) and most were women (19/21). The average time from start of treatment to fracture diagnosis was 6 years (Table 1, 2). One patient had received treatment with risedronate. Two had received intravenous zolendronate once yearly, but both had a previous history of oral bisphosphonate use. The remaining 18 patients had used alendronate. Based solely on the ADR case narratives ten (48 %) of the 21 cases in group A were described as having experienced prodromal symptoms and none were mentioned for the remaining cases. After reviewing the medical records, however, prodromal symptoms had been documented for 18 cases; i.e., for 86 % (95 % CI 64–97 %). Based on the duration of symptoms (Table 4) the cases were divided into six categories: "days" (<14 days); "weeks" (<2 months); "months" (>2 months); ">1 year;" "unknown duration;" and, "no symptoms or no documentation of symptoms." Among the 18 with documented symptoms 15 were reported to have been present for weeks or longer before the fracture actually occurred. Description of the prodromal symptoms (Table 2 and 4) was provided for 17 of the 18 cases and commonly consisted of pain in the ipsilateral thigh ($n = 14$). In addition to thigh pain five patients reported pain in the hip, knee or groin. In five cases the thigh pain was reported as having intensified weeks or days prior to the fracture and in four cases increased loading led to increased pain.

Table 2 Detailed data for the verified group A ($n = 21$)

Age (y)	Sex	Substance and duration of use prior to AF	Factors initiating the AF	Prodromal symptoms present	Duration of prodromal symptoms	Location of the prodromal symptoms
79	female	alendronic acid	spontaneous	yes	weeks	ipsilateral thigh
70	female	alendronic acid 6y	spontaneous	yes	weeks	ipsilateral thigh and knee intensified days prior to the fracture
76	female	alendronic acid 5y	spontaneous	yes	months	NA
62	female	alendronic acid 5y 6m	spontaneous	yes	months	ipsilateral thigh and groin
70	female	Risedronic acid 4y	spontaneous	yes	1 year or longer	ipsilateral thigh intensified with increased loading
62	female	alendronic acid 10y	low energy trauma	unknown[a]	NA	NA
71	female	alendronic acid 5y	spontaneous	yes	months	ipsilateral thigh
71	female	alendronic acid 5y	spontaneous	yes	days	ipsilateral thigh intensified with increased loading
64	female	alendronic acid 2y	spontaneous	unknown[a]	NA	NA
83	female	alendronic acid 7y	spontaneous	yes	weeks	ipsilateral thigh intensified with increased loading intensified prior to the fracture
73	female	alendronic acid 10y	spontaneous	yes	weeks	ipsilateral thigh intensified two weeks prior to the fracture
88	female	alendronic acid 11m	NA	yes	months	ipsilateral thigh
58	female	alendronic acid 5y	low energy trauma	yes	NA	both thighs
78F	female	alendronic acid 7y	low energy trauma	yes	months	ipsilateral thigh intensified three months prior to the fracture
60	female	alendronic acid 2y	spontaneous	yes	months	bilateral in thigh and groin
77	female	alendronic acid 10y	spontaneous	yes	months	ipsilateral thigh intensified with increased loading
73	female	alendronic acid 9y	low energy trauma	yes	NA	both thighs
68	male	zolendronic acid 2y (previously long duration of treatment with oral bisphosphonates)	spontaneous	yes	months	ipsilateral leg and the lower back
80	female	alendronic acid 8y zolendronic acid 1y	NA	yes	1 year or longer	ipsilateral thigh and hip
63	male	alendronic acid 3y 9m	spontaneous	unknown[a]	NA	NA
69	female	alendronic acid 8y	low energy trauma	yes	1 year or longer	ipsilateral hip intensified two days prior to the fracture

[a] no discussion was available on possible prodromal symptoms in medical records, NA not available

For the 24 patients in group B (Table 1 and 3) we had no access to medical records, and clinical data were only available from the report received by the MPA (from the reporting physician) and which had been noted in the case narrative by the clinical assessor at the MPA. Based on the available data eleven patients (46 %) had experienced prodromal symptoms while there was no documentation or any comments about the possibility of such symptoms for the remaining 13 cases, which is in agreement with group A. Patient age ranged from 49–89 (mean 74.5), and all were women. The average time from initiation of bisphosphonate treatment to fracture diagnosis was 6.5 years

Table 3 Detailed data for the non-verified group B (n = 24)

Age (years)	Gender	Substance and duration of use prior to AF	Factors initiating the AF	Prodromal symptoms present	Duration of prodromal symptoms	Location of the prodromal symptoms
75	female	alendronic acid 7y	spontaneous	unknown[b]	NA	NA
56	female	risedronic acid 8y	spontaneous	yes	months	NA
84	female	alendronic acid 5y	low energy trauma	unknown[b]	NA	NA
49	female	alendronic acid 6y	spontaneous	unknown[b]	NA	NA
75	female	risedronic acid	low energy trauma	unknown[b]	NA	NA
88	female	alendronic acid 3y	NA	yes	NA	both thighs
82	female	alendronic acid 3y	low energy trauma	unknown[b]	NA	NA
77	female	alendronic acid	low energy trauma	yes	days	ipsilateral knee
86	female	alendronic acid	spontaneous	yes	weeks	ipsilateral hip
88	female	alendronic acid 5y	low energy trauma	unknown[b]	NA	NA
89	female	alendronic acid 2y	NA	unknown[b]	NA	NA
64	female	alendronic acid 10y	spontaneous	yes	1 year or longer	ipsilateral thigh
83	female	alendronic acid	low energy trauma	yes	weeks	ipsilateral hip
74	female	alendronic acid	NA	unknown[b]	NA	NA
66	female	alendronic acid 4y 8 m	NA	unknown[b]	NA	NA
64	female	alendronic acid 9y	NA	no[a]	NA	NA
78	female	alendronic acid 12y 9 m	NA	yes	weeks	ipsilateral thigh
83	female	alendronic acid 8y	low energy trauma	yes	weeks	NA
62	female	alendronic acid	low energy trauma	unknown[b]	NA	NA
74	female	risedronic acid 9y	low energy trauma	yes	1 year or longer	ipsilateral hip
68	female	alendronic acid 9y	low energy trauma	yes	months	ipsilateral hip
81	female	alendronic acid 3y	low enegy trauma	yes	NA	ipsilateral thigh
67	female	alendronic acid	spontaneous	unknown[b]	NA	NA
75	female	alendronic acid	spontaneous	unknown[b]	NA	NA

[a] presence of prodromal symptoms were explicitly denied in medical records

[b] no discussion was available on possible prodromal symptoms in medical records

NA not available

(data available for 17). Three patients had received treatment with risedronate and the remaining 21 with alendronate.

The proportion of patients with prodromal symptoms based on only ADR case narratives (from both group A and B) was thus 47 % (21 out of 45), which shows a substantial underreporting.

Discussion

Although AF was first described in the literature in 2005 [1], the mechanism behind the pathology has still not yet been fully elucidated. The prevailing theories suggests that continued bisphosphonate therapy leads to impaired microcrack healing [3, 4] and prolonged suppression of bone remodelling, eventually causing increasing microdamage, predisposing the skeleton to AF [6–9].

Our results indicating a high prevalence of prodromal symptoms in atypical fracture cases are supported by previous investigations. Studies have reported frequencies ranging between 50 and 77 % [10–14]. Such discrepancies can also be observed among reported case series: 5/5 [15]; 4/7 [16]; 5/9 [6]; and, 7/16 [17]. The American Society for Bone and Mineral Research (ASBMR) task force reviewed the literature and concluded that approximately 70 % of patients with an AF had a history of prodromal symptoms [2]. The most recent ASBMR task force report [3] suggested prodromal symptoms as a minor feature in the definition of AFs. Our results suggest a frequency of prodromal symptoms of 86 %. Obviously, for most studies underreporting of prodromal symptoms may lower the frequency and hence an average of $\geq$75 % is a realistic figure.

Discrepancy in the reported frequency of prodromal symptoms among different studies (including the present study) may depend on several factors. To our knowledge the present study is the first to be entirely devoted to investigating prodromal symptoms among patients with AF. Hence, the patients' medical charts were searched for

Table 4 Characteristics of the 45 (21 verified and 24 non-verified) patients included in the study, stratified by duration of prodromal symptoms

Duration of prodromal symptoms	Days		Weeks		Months		1 year or longer		Unknown duration		No symptoms	
	VER	NON-VER	VER	NON-VER	VER	NON-VER	VER	NON-VER	VER	NON-VER	VER	NON-VER
n	1	1	4	4	8	2	3	2	2	2	3	13
Mean age (years)	71	77	76	82	73 62		73	69	66	84	63	73
Mean duration of bisphosphonate therapy until fracture diagnosis (years)	5	NM[c]	6 ($n = 3$)	9 ($n = 3$)	5 (n = 7)	8	7	9	7	3	5	5 ($n = 8$)
Fracture trigger	1 spon[a]	1 LET[b]	4 spon	2 spon 2 LET	6 spon 1 LET 1 NM	1 spon 1 LET	1 spon 1 LET 1 NM	2 spon	2 LET	1 LET 1 Nm	1 spon 2 LET	4 spon 6 LET 3 NM

[a] spontaneous

[b] low energy trauma

[c] Not mentioned

documentations of prodromal symptoms. This is in contrast to the majority of previous studies where prodromal symptoms were more of a secondary objective, only reported if encountered rather than actively searched for. In the present study medical charts were not restricted to a specific hospital, institution or department. Nor were they limited to the time frame of the emergency visit to the orthopaedic department due to the AF. Instead, we included charts from both general practitioners and specialty hospital departments. Hence, part of the reason behind the reported discrepancy of prodromal symptoms is likely caused by different investigational approaches. Seemingly a more in-depth and broad investigation into the patients' medical records and history may lead to an increased possibility of detecting documentation supportive of prodromal symptoms [10].

Some authors stress the importance of evaluating long-term bisphosphonate users with unexplained thigh or hip pain [10]. However, since cases of AF have also been reported with bisphosphonate treatment duration of <2 years [4] we believe that such evaluation should not only be restricted to those with longer-term use (more than 5 years). Among the patients within the present study 28 % (group A and B combined) used bisphosphonates for <5 years (data available for 36 patients).

Our study is based on spontaneous reports from physicians on a nationwide level. Nonetheless, analysis of radiographs and medical records revealed a high diagnostic accuracy. Without access to medical records for the 21 cases in group A prodromal symptoms were reported among 10 cases (48 %). When reviewing their medical records we found documented prodromal symptoms in 18 cases, almost double the frequency (86 %). Hence, without access to medical records the frequency of prodromal symptoms was comparable between group A (48 %) and B (46 %). This shows that the frequency of prodromal symptoms of an AF based on information received by health care authorities through spontaneously reported ADRs are very likely to be lower than the actual frequency. Not reporting such symptoms may be due to a general unawareness among health care professionals about the association between prodromal symptoms and AFs.

As reported herein eleven out of 18 patients (group A) had prodromal symptoms for months or longer than a year prior to the fracture. Others have also reported prodromal symptoms debuting months prior to the fracture [4, 6, 18]. These periods allow the physicians to take measures that may possibly reduce the risk of an AF.

Atypical fractures needs to be correctly classified [2] in order to establish the association with bisphosphonate. Nevertheless, although less frequently, atypical fractures of the femur do also occur in both women and men without previous bisphosphonate use. We did not examine this small subgroup of patients, which is also a limitation of our study.

Patients undergoing bisphosphonate therapy presenting with the type of symptoms reported here should be evaluated with radiography. This can be performed with plain radiographs or preferentially with magnetic resonance imaging or computerized tomography scans. In cases with confirmed radiographic findings antiresorptive agents should be discontinued. The half-life of bound alendronate in the skeleton is longer than 10 years [19] and it has been shown that discontinuation of alendronate treatment after

5 years does not appear to significantly increase the risk of osteoporosis-related fractures [20] but that discontinuation of the drug leads to a fast decline in terms of risk of an AF [4]. Supportive care should be optimized and patients may benefit from the use of a wheel chair. The patient should be re-evaluated after three months. If there is no clinical (reduced symptoms) or radiographic improvement prophylactic nail fixation should be considered [3]. Prophylactic nail fixation should also be considered in cases where the initial radiographic examination reveals an incomplete fracture [3].

Recently there have been numerous reports observing the benefits of using anabolic treatment with teriparatide (TPTD) in the management of AFs [21–23]. Seemingly TPTD treatment may also be helpful in pain reduction [22]. Although TPTD might be considered beneficial in the prevention of AF, there is presently insufficient evidence to recommend routine use [3].

Investigations and treatments initiated on the basis of the prodromal symptoms may possibly reduce the risk of an AF in the affected limb but also in the contralateral limb since AFs are often reported to be bilateral [15, 24]. Interventional efforts may lead to succesful healing of an incomplete atypical fracture [21–23, 25]. However, one must remember that bisphosphonates are indeed useful for the prescribed patient. Hence discontinuation must be carefully evaluated against the patient's overall skeletal condition and each case needs to be considered individually.

As shown here and previously by others the frequency of prodromal symptoms is high among patients developing an AF. Awareness of such symptoms may facilitate early diagnosis and possible prevention of the AF. Hopefully future studies will increase our understanding on how prodromal symptoms should be interpreted when combined with other findings.

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Conflict of interest All authors have no conflicts of interest.

Ethical approval Ethical approval was granted from the Regional Ethics Committee, Uppsala, Sweden (2011/231).

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