Clinical Practice Article

Atypical Femoral Fractures Following Use of Intravenous Zoledronic Acid After Prior Treatment with Alendronate: A Clinical Practice Series and Opinion

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Abstract

Aims: An increasing number atypical femoral fractures (AFFs) have been reported in patients who have taken bisphosphonates (BPs) for several years. The European Medicines Agency (EMA) concluded in 2011 that these fractures were a class effect of the drugs. The United States Food & Drug Administration (FDA) updated labels for currently proprietary intravenous Reclast™ (zoledronic acid) have, since 2015, agreed with the EMA opinion. Section 17 of the FDA label states Reclast™ “can cause” these fractures. In this report, we present a clinical sub-class of cases of these fractures illustrating the potential for harm associated with switching BP therapy from an oral agent to Reclast™ (zoledronic acid).

Methodology: This paper presents 6 long-term case descriptions of patients, diagnosed with either osteopenia or osteoporosis, incurring a total of ten AFFs following a switch to intravenous zoledronic acid after a much longer and uncomplicated period on orals BPs. One additional case is presented to illustrate that AFFs may also occur with intravenous therapy alone. We have collected these cases directly from the patients and have confirmed all of the details by access to the original medical records, including the radiology and surgery reports. Our opportunity for access is fully described in the article.

Results and Opinion: Such a switch has never been investigated in a clinical trial. Based on the pharmacokinetics associated with the intravenous routes for these drugs, we present our reasoning why the untested therapy exemplified should be considered as potentially hazardous. Furthermore, we discuss the reported but rather unremarked wide individual variation in the rate of elimination of intravenously-administered BPs which may be an important factor in determining which individuals are at greatest risk of incurring an AFF.

1. Introduction

We have had occasion, as previously described [1], to provide counseling and support to persons with bisphosphonate-associated atypical femur [2,3] and atypical non-femur [4] fractures through a private organization established by Jennifer Schneider in 2007 after she recognized that there were very few sources of information and support for these individuals. Admission to the group requires documentation that the applicant has incurred a fracture with the clinical and anatomic details associated with the AFFs. This organization led to our publication in 2012 of a statistical summary [1] of the antecedent circumstances and subsequent morbidities of a sub-group of this membership - 81 patients, whose fractures had occurred between 2001 and mid-2011. Because of our steady accumulation of details of individual entire pre- and post-fracture experiences, which never appear together in any single medical record, we have had the opportunity to note trends that otherwise might not have been obvious. We have noted, for example, many types of bisphosphonate-associated fractures in addition to the atypical femur fractures [5], sometimes occurring in the same individual with an AFF. One of these trends, providing insight for clinical practitioner into the impact of differing pharmacokinetics of otherwise similar medications is reported here. The material presented in illustration of this trend has all been confirmed by examination of the associated original medical records.

The medicinal chemist and pharmacologist generally consider the potential mechanism of action of a specific molecule at the molecular or cellular level of interest in the search for a potential new medication. Decisions about the route of administration and the dosing are sometimes left to specialists in other fields. The BP medications currently approved by the FDA for the treatment and prevention of osteoporosis were discovered following the realization [6,7] that pyrophosphate (pyrophosphoric acid at physiologic pH) played an important role in the control of calcium metabolism. How this discovery led by a variety of steps and missteps to the introduction of the BP medications has been recently reviewed [8].

The pivotal clinical trials which were presented for FDA approval of the BPs alendronate [9,10] and zoledronic acid [11] shared quite similar designs. Carefully selected cadres with specified baseline characteristics were randomized to drug or placebo over periods of approximately three years. None of the publications of these pivotal trials reported any unusual femoral fractures. One possible explanation is the small size, carefully chosen subjects (58% of the originally screened persons were excluded from the zoledronic acid pivotal trial), and short duration of these studies. Reexamination of a limited group of

the trials some years after approval did uncover one previously unreported case of bilateral femoral shaft fractures [12] in the drug arm.

Our 2012 statistical summary of the experiences of 81 persons incurring one, two, or more bisphosphonate-associated atypical [1] femur and non-femur fractures included one individual who was prescribed zoledronic acid infusion for the osteoporosis indication. This patient had not taken any prior anti-osteoporosis medication. Zoledronic acid was approved in 2007 by the FDA for the treatment of post-menopausal osteoporosis and in 2009 for the prevention of osteoporosis for post-menopausal women with low bone mass.

In our statistical series, the initial oral bisphosphonate-associated femur fractures occurred after an average treatment of 9.1 years (range 1.5-17). Other studies have produced similar ranges [2] but even short-term use incurs some increased risk, as can be detected in large statistical analyses [13]. Utilization assessments [14,15] of the BPs have shown very poor "compliance" in the sense of regular continuation of the prescribed medicine. In our own experience as well as reports by others, it is quite common for even the compliant patient to fail to follow the detailed method of consumption necessary to achieve a meaningful drug effect [16]. The use of intravenous (IV) zoledronic acid, the effect of a single dose persisting for 1-2 years, to circumvent the documented failure to persist with oral BPs, was argued in early descriptions of its clinical efficacy [17]: "Oral BPs are widely used for treating osteoporosis … [h]owever, they do have limitations related to long-term compliance…. Intermittent intravenous administration of BPs might address some of these problems." The publication describing the original pivotal HORIZON zoledronic acid osteoporosis trial [11] makes the same point: "Poor adherence has been shown to compromise the effectiveness of treatment against fracture and to increase the costs of medical care. A single infusion of intravenous zoledronic acid has been reported to decrease bone turnover and improve bone density for at least 12 months after infusion, suggesting an enduring effect." This argument does not appear in the current label [18].

2. Materials and Methods

A subset of the individual longitudinal histories documented by us has been noted to have included relatively long but uncomplicated treatments (range 6 to 10 years) with oral agents, predominantly alendronate, followed by switching for varying reasons to intravenous Reclast™ (zoledronic acid), with the patient then subsequently suffering one or two AFFs (range 4½ months to 2 years after the last infusion). Some of the individuals in this subset have expired or have been otherwise lost

to follow-up; however we report on seven patients who incurred a total of 12 AFFs which occurred only during or after the Reclast™ (zoledronic acid) phase of therapy. Weobtained satisfactory hospital and medical office records and imaging evidence confirming these events. These seven extended case histories are presented here as individual illustrations of our contention that the change itself is likely to have contributed to the outcome.

3. Results

A brief extended historical narrative of each illustration is followed by a chart summarizing the most salient points. All the patients described are female.

Case 1. This patient with long-standing rheumatoid arthritis was prescribed alendronate from age 63 to age 70 for low bone density, then oral ibandronate for a year. There was no improvement in her bone density scans. Her rheumatologist switched her to Reclast™ (zoledronic acid) and she subsequently received 3 annual infusions. At age 73½, about 6 months after the final infusion, she experienced a spontaneous oblique non-comminuted fracture of the left femoral shaft. The post-operative radiology images show a slight thickening in the lateral cortex. Her surgeon commented in her chart: "...follows up on her left femur fracture status post IM rodding …. She had mentioned she thought it was related to one of her osteoporosis medications though I don't see an obvious lateral sided stress reaction, stress fracture. It is not clear to me why she had a fracture."

Approximately 4 weeks later, she consulted the same surgeon about a severe pain in the contralateral (right) femur. A radionuclide scan was obtained showing "small focus of moderate tracer localization to the lateral cortex of the right femur at the junction of the proximal and middle thirds..." A right side plain film 9 weeks after the initial left femur fracture showed only a distinct lateral cortical reaction in the right femur. ~~; there was no fracture line evident in the version we obtained.~~ An increased reaction was seen in a film done 16 weeks after the initial fracture and a post-surgical rodding film at 19 weeks clearly shows an undisplaced fracture line through the lateral cortex. Figure 1 shows the initial completed right fracture after repair. Figure 2 shows the left cortical reaction before surgery, Figure 3 is an inverted view with enhanced contrast showing the non-displaced fracture line more clearly. These images are characteristic examples of the AFF.

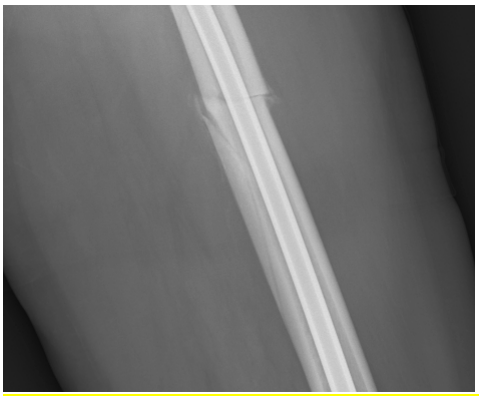

Figure 1

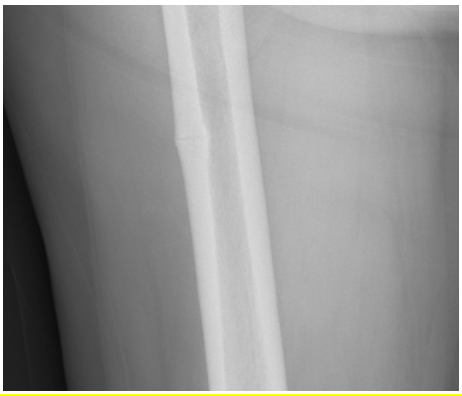

Figure 2

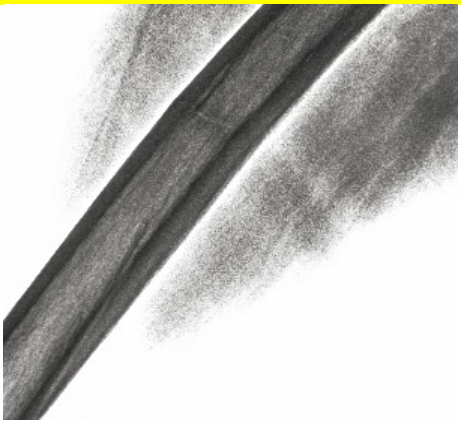

Figure 3

Case 2. After an initial diagnosis of osteopenia, this patient was treated with alendronate for 10½ years, from age 63½ to age 74. She was then given a single infusion of Reclast™ (zoledronic acid). Three months later, she developed severe pain in her left femur. A radiologist reported that a 2-view series of the femur revealed “no fracture or worrisome lesion”. She saw an orthopedic surgeon 2 weeks laterwho performed a physical examination and diagnosed lumbar radiculopathy.
Four days after that visit and 4½ months after the infusion, she suffered a subtrochanteric complete fracture while walking with a supporting cane on a level floor in her home. No additional imaging studies of the femur were done before the completed fracture. She saw six specialists during the post-infusion pain interval. She reports that none of them even mentioned a possible connection between the BPs and her leg pain. Seven months after the AFF, she experienced a fracture of a pubic bone. She was still scheduled for a second Reclast™ (zoledronic acid) infusion 12 months after the first one, but refused this option.

Case 3. After a diagnosis of osteopenia at age 48, this patient was started on alendronate. At age 54, she was given one infusion of Reclast™ (zoledronic acid). When she was almost due for her next infusion, after having six months of left leg pain, she incurred a left subtrochanteric femur fracture while walking in her home.
The only images available are cross-table laterals done in the operating room. These revealed a slightly oblique non-comminuted break with beaking. The fracture healed readily without complications after the IM rod was placed. She

received no more bone-active medications. At age 60, a healing tibial fracture was discovered by X-ray. No trauma was associated with the onset of lower leg pain preceding this diagnosis. Shortly thereafter, Forteo™ was prescribed but was discontinued after two months due to a rash. At age 62, she incurred an atraumatic right transverse mid-shaft femur fracture. The preoperative film shows the characteristic lateral origin, beaking, and cortical reaction. This second fracture was 8 years after her single Reclast™ (zoledronic acid) infusion.

Case 4. This patient had surgical menopause at age 33. At age 44 she was started on alendronate because of low bone mineral density and continued it for 10 of the subsequent 12 years. A progress note written when the patient was encouraged at age 55 to restart alendronate for the last two years of the 10 stated: “She previously was on Fosamax (alendronate) but did not take it regularly. She said it was hard to take because she was really in the habit of eating first thing in the morning.” This concern was apparently pursued because at age 57¼, she was given an infusion of Reclast™ (zoledronic acid). Six months later she incurred an atraumatic “proximal femoral diaphyseal angulated fracture”, additionally described as slightly oblique and not comminuted. In contrast to most of these illustrations, her medical team immediately acknowledged an association between the fracture and the BP medications.

Case 5. Beginning at age 54, when osteoporosis was diagnosed, this patient took alendronate for 10 years, during which time her osteoporosis persisted. When she was 66, she was started on Reclast™ (zoledronic acid) for a total of 2 infusions, the last being given when she was about 69¼ years of age. She was told the infusions were needed because she had decreased bone mineral density. Approximately eight months later, when she was almost 70, she incurred an atraumatic right femoral fracture after several months of right thigh pain. She underwent retrograde IM nailing. Her surgeon commented in the operative note: “Assessment of the patient's x-rays reveals an unusual appearing femur fracture in that it is very horizontally or transversely oriented and there is bony sclerosis adjacent to the fracture site and some thickening of the cortex along the medial aspect of the femur. I explained to the patient that the fracture does not look like a typical femur fracture and had a relatively low energy mechanism, and therefore, may represent an atypical femur fracture from medication such as Fosamax and Reclast….” Several months later she developed pain her left thigh. An x-ray showed “an area of cortical thickening in the mid lateral femur and a faint lucency consistent with an early stress fracture.” According to her orthopedist’s note, the endocrinologist recommended surgery, but the orthopedist advised a conservative approach, which is the one she followed.

Case 6. This patient was prescribed alendronate when she was 36 years of age. At that time, the bone mineral density of the total hip and lumbar spine gave T-score results of -2.6 and -2.8 respectively. Her history differs from those of the foregoing patients’ illustrations but it is inserted here because of the

exceptional circumstances which it illustrates. She was not menopausal at the time of alendronate initiation. Physically, she was short and thin with smaller than average bones.

The oral BP treatment was continued until age 42 and then 2 years of Forteo™ prescribed. There was very little bone density response to the alendronate. She had incurred no fractures at this time. There continued to be no significant bone mineral density improvement after the Forteo™. Reclast™ (zoledronic acid) infusions were begun at age 45 and about 1½ years after the third infusion, Prolia™ (denosumab) was begun at age 48½ and continued for 4 injections. Just a few days before her 50th birthday, and eleven days after the 4th Prolia™ injection, she incurred an atraumatic transverse subtrochanteric left femoral fracture with a horizontal starting zone through a thickened lateral cortex with pronounced beaking. This fracture is illustrated in figure 4. One week after her IM rod repair, a right femoral undisplaced fracture originating laterally and associated with a cortical reaction was diagnosed and similarly repaired.

We previously reported an almost identical sequence of events in another individual [19].

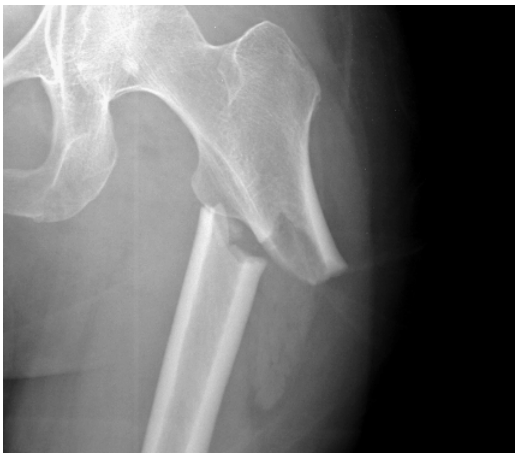

Figure 4

Case 7. This patient did not take an oral BP. She is included to illustrate that such pretreatment is by no means a requirement for incurring an AFF after Reclast™ (zoledronic acid) infusion. She received her first infusion at age 62 and her fifth one at age 66¼. Eleven months later she sustained a transverse non-comminuted fracture in the upper portion of the right femoral shaft.

Five weeks after the initial fracture she consulted her prescribing physician about continuing pain. The physician records in his note that she had sustained a hip fracture [sic] and suggested Forteo™ (teriparatide). She then apparently consulted the Emergency Department. The next day a radiologist reported "There is mild thickening of the lateral cortex of the proximal shaft of the left femur with a faint lucent line laterally in the cortex. This suggests a tiny incomplete fracture. This is at the same location as a prior fracture of the right proximal femur. This location in [sic] is seen with BP therapy. This suggest [sic] an impending fracture." A second series a day later confirmed this: "There is *again* [our emphasis] a focal area of cortical thickening involving lateral aspect of the proximal femoral shaft. There is also small amount of periosteal reaction at the same level medially. Impression: focal areas of periosteal reaction/thickening proximal femur. This type of appearance can be seen with impending/stress fracture due to BP treatment." Surgical intervention with IM rodding followed on the same day.

Chart 1 summarizes the above illustrations. The year of the first fracture is included to place the cases in temporal context.

Case	Oral BP	Reclast	Fracture 1 (Calendar year of fx)	Character	Fracture 2	Character	Comment
1	7 years	3 infusions	6 months after 3rd Reclast (2015)	Short oblique mid-shaft complete	7 months after 3rd Reclast	Lateral cortex mid-shaft incomplete	
2	10½ years	1 infusion	4½ months after the 1st infusion (2010)	ST transverse complete			Pubic ramus fracture ~1 yr after the infusion and 1 Jones fracture on alendronate and two more after the Reclast (cf. ref 4)
3	6 years	1 infusion	11 months after the 1st infusion (2010)	Mid-shaft transverse complete	8 years after the only Reclast	Contralateral (right) mid-shaft transverse,	One tibial fracture 6 years after the Reclast (cf. 4)

					infusion.	complete	
4	10 years	1 infusion	6 months after single infusion (2013)	Proximal diaphyseal angulated complete			
5	10 years	2 infusions	8 months after last infusion (2016)	Rt femur shaft transverse cortical rxn complete	20 months after last infusion	Left femur insufficiency fracture confirmed by MRI incomplete	Continues at time of this publication on Forteo without surgery on second fx
6	6 years	3 infusions followed by 4 injections of Prolia	2 years after last infusion; 11 days after last Prolia Injection (2013)	ST transverse complete	One week after first fracture	Contralateral ST lateral origin cortical reaction Incomplete rodded	Forteo for 2 years after the alendronate and before the Reclast
7	n/a	5 infusions	11 months after the last infusion (2015)	Upper shaft transverse, complete	Five weeks after first fracture	Contralateral upper shaft lateral origin incomplete cortical rxn	

Chart 1

4. Discussion

Since many persons have been reported to have had AFFs after treatment with oral BPs alone, it is not possible to partition responsibility for the six combination events described above between the different agents. We report these to illustrate that a change from one strong antiresorptive to another is no guarantee of added benefit but has potential for harm.

When a clinician decides to abandon therapy with one agent in favor of another, it is commonly assumed that the effects of the first agent will be metabolically dissipated in a timely manner. The bisphosphonate drugs are almost unique in not conforming to this paradigm. In the pivotal zoledronic acid trial noted above, a candidate subject who had taken a BP was required to have a “wash-out” interval of up to two years prior to participation. Such a requirement illustrates a failure to understand the metabolism of these drugs even by the designers of

these important trials. It has been known for several decades that these drugs are not metabolically degraded, are excreted unchanged, and remain resident in the skeleton for many years [20]. Furthermore, if the change is from an oral bisphosphonate to intravenous treatment, this may *de facto* amount to a significantly more potent dose. Many authors have described the poor compliance associated with oral BP medication [15,16]. This has been attributed to the inconvenience of the required mode of consumption involving drinking water and water only (since it has been long known [17] that these compounds can bind tightly to minerals found in other food and drink, thus preventing intestinal absorption) and may also be due to the esophageal/gastrointestinal irritation [18] some individuals experience (the reason for the additional requirement of remaining upright following the oral dosing). While it is evident that these kinds of failure to persist in the prescribed use of the drug are avoided by substitution of the intravenous route, we feel that the documented hesitancy to comply with the instructions for use with the oral drugs may in fact protect many persons from the serious long-term complications of the BPs, notably the associated femur fractures. These illustrations document what may happen when this hesitancy is circumvented.

In our 2012 review [1] of 81 patients with AFFs, we found that 77% reported prodromal pain, but only 16% of them were diagnosed as stress fractures before they proceeded to complete fractures. The importance of this finding is that when leg pain in a patient on long-term BP is recognized as a warning sign and a diagnosis of a stress AFF is considered, confirmation of that diagnosis and treatment at that stage (along with stopping the BP) is the best way to prevent a complete fracture. Physicians who prescribe BPs or denosumab (the advisory literature accompanying denosumab contains a specific warning about thigh pain) should recognize the significance of thigh pain in such patients. Yet in several of these present cases the connection between thigh pain and an impending fracture was evidently not considered. In our 2012 study 44% of patients who sustained a complete AFF were continued on their BP, which led to an increased risk of a contralateral AFF compared to cases in which the BP was stopped. Among the illustrations above, one patient who suffered an AFF several months after her first Reclast™ (zoledronic acid) infusion was nonetheless scheduled for a second infusion. In the 2012 study, 40% of the patients continued on post-fracture BPs experienced a contralateral AFF.

Physicians should not recommend continuation of BP treatment in patients who have already fractured one femur. Similarly, although it is generally accepted that the risk of an AFF increases with the length of time on an antiresorptive drug, a patient who does not appear to be benefiting from one BP should not be

advised to continue the drug or switched to another BP, which merely continues a trial of the same mechanism of action. Although the trials of long-term BP use do not provide evidence of efficacy beyond 5 years [21, 22], many patients are maintained on BPs for a decade or more, using the paradigm of expected rapid drug metabolism. It has been many years since the warning [23] that prolonged use may be associated with increased fractures was first published. Six of our illustrations exemplify the use of a new antiresorptive medication when the long-term use of another of the same class of drugs was deemed unsatisfactory. Furthermore, none of the cases was associated with any major fractures on the oral BP, in which case an ongoing need at least might have been deemed desirable.

This induction of increased risk associated with the longer use of drugs that are identical in their mechanism of action is compounded by the near-universal dependence on sequential bone mineral density as a measure of effectiveness. The World Health Organization (WHO) criteria for osteoporosis were designed for *post-menopausal* analysis (24) and the use of BPs before menopause has never been studied even in a safety trial. Additionally the insensitivity of the dual x-ray absorptiometry (DXA) to extremes of body mass is well-known, and this tool tends to underestimate bone density in petite women with small bones (25). We believe that no provider should order a DXA study without being aware of the influence of body mass on the results (26).

The greater part (82%) of the *incidence*, in contrast to the *rate*, of low-energy spontaneous fragility fractures is not predicted [27, 28] by use of the WHO bone mineral density criterion for osteoporosis. Furthermore, none of the BP class of drugs has been shown to effect a statistical reduction in clinical, i.e., symptomatic, fractures [10] in patients with osteopenia despite the approval for the class for use in prevention of osteoporosis in persons with low bone mass, i.e., “osteopenia”.

Finally we return to the issue of differing pharmacokinetics of the oral and intravenous BPs. There is surprisingly little published information about this important subject. Khan et al. reported [29], after the FDA approval of alendronate, an open trial of 21 postmenopausal women with osteoporosis. These individuals were given an *intravenous* infusion of 7.5 mg of alendronate in 500 cc saline over 12 hours on four consecutive days. They were followed in a metabolic laboratory in-patient setting for a week and then periodically over 2 years as outpatients. The cumulative excretion of the initial 30 mg dose of the drug varied widely among the 11 individuals evaluated. The range of the terminal half-life, indicating the calculated amount of time that would be required

for half the original dose to appear in the urine, was 2.7-17.4 years. The mean was 10.5 years. The drug not excreted was presumed to reside in the bone. Very little has been said about this 6.4-fold variation in the retained drug. We suggest that it may contribute to the sporadic incidence of the AFFs, with the slower excreters being more likely to suffer the fractures.

The distribution of the BPs in the skeleton is not uniform [30]. Uptake (and release) is faster in bones with higher remodeling rates, such as the alveolar bone proper which holds the teeth, compared to the mid-diaphyseal femur [31]. Conversely, this means the turnover rate in the cortical femoral shaft is relatively low, suggesting that the uptake of BPs there would be slower to occur but also slower to be released. This may affect the localization of the atypical fractures in such bones. The known longest zone of maximum tensile force on the femur is located at the lateral area of initiation of the atypical fractures [32]. Combining this fact with a BP retention longer than the average overall skeletal retention may well contribute to the particular localization of these fractures and the occurrence in some individuals but not in others.

With oral alendronate, the concentration in the plasma was too small to measure in the referenced human studies [33]. The pharmacokinetics of zoledronic acid have been publicly reported [34], insofar as we can tell, only in a small group of individuals treated for malignant metastases with monthly doses. In contrast to alendronate, zoledronic acid could be detected in the serum for 28 days. Remarkably, this observation was used to rationalize the monthly use of the drug in this context. The terminal half-life of zoledronate was not reported.

Some inferences regarding relative clinical potency can be drawn. Zoledronic acid exhibits the greatest affinity of all the BPs for the hydroxyapatite which constitutes the major portion of the hard tissue of bone [35]. A bisphosphonate must be bound to bone in order to be presented to the target osteoclast.

The measured [36] IC50 inhibition concentration of farnesyl pyrophosphate synthase (FPPS), the target enzyme for the BPs, has been shown for zoledronic acid to be roughly equivalent or slightly more potent than that of risedronate, which in turn is significantly more potent than that of alendronate [37].

The clinical potency of the BP drugs is multifactorial since several semi-independent events are involved in the mechanism of action at the tissue level. However, it is clear that zoledronic acid exceeds alendronate in affinity for

bone mineral and in potency of inhibition of FPPS, two important factors in the chain of events leading to osteoclast inhibition.

5. Conclusions

The illustrations provided indicate that a switch from one BP to another in search of an elusive increase in the bone mineral density or an improvement in compliance can prove hazardous. The results of the BP mechanisms of action at the tissue level may appear to be qualitatively similar but there is substantial evidence that there are quantitative differences of potency at each step of the process. Furthermore, no trials have assessed the safety of such a switch, much less the efficacy of it.

Beyond that, the use of the bone mineral density as the ultimate criterion of drug effectiveness has been challenged at many levels, including the lack of any correlation with the *incidence* of fragility fractures despite the evident relationship between bone mineral density and fracture *risk*.

Five of the 7 patients sustained their first or only AFF between 2013 and 2016, recently enough that clinicians might have been expected to be aware of the connection between long-term BP use and AFFs. Failure even to consider the possibility of an incipient fracture of the femur, when a patient reports leg pain, seems to stem from the lack of perception of this danger signal in association with concurrent or prior BP therapy. This suggests that the charted medicine list should always include whether or not the individual *ever* was treated with this class of medication. Appreciation of the unique qualities of these drugs -- long skeletal retention and no metabolic deactivation -- is difficult because there is no precedent for expecting such characteristics in a prescribable medication, with the possible exception of strontium, which is not approved for these uses by the FDA.

Finally, the importance of evaluation, even in the absence of associated pain, of the contralateral femur after an atypical fracture has also been illustrated, as well as the potential inadequacy of a simple X-ray series to detect an incipient fracture.

Abbreviations used in text
IM = intramedullary

FDA = United States Food & Drug Administration
EMA = European Medicines Agency
BP = bisphosphonate(s)
DXA = dual x-ray absorptiometry
MRI = magnetic resonance imaging
For “osteopenia” and “osteoporosis”, the WHO 1994 bone mineral density based definitions are used. That definition also assigns the osteoporosis status to a person with a prevalent fragility fracture no matter what the bone mineral density.
IV = intravenous

Competing Interests

Author WBH as served as an expert witness in litigation concerning the BP drugs. Author JPS declares that she has no competing interests.

Authors’ Contributions

The authors contributed equally to the production of this paper. Author WBH wrote the original manuscript. Author JPS was personally responsible for the challenging task of securing all the official medical records. Both authors contributed equally to the editing of the final draft. Both authors have approved the final manuscript.

Individual Permissions

The authors attest that they have both examined the original medical records and have presented the material in these records in as detailed a fashion as possible consistent with concealment of all patient identity information. Each of the subjects of these records has provided a signed release allowing us to publish her history in full detail so long as no personal information is disclosed.

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