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The role of zoledronic acid in the treatment of post-menopausal osteoporosis.

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ABSTRACT

The purpose of this mini review is to assess the efficacy and safety of zoledronic acid in the treatment of post-menopausal osteoporosis. Osteoporosis is the commonest metabolic bone disease, characterized by decreased bone mass and poor bone quality, resulting in increased risk for fracture. Zoledronic acid is a third-generation nitrogen-containing bisphosphonate used for the treatment of osteoporosis. It is used intravenously once a year and it has been proven to be effective, safe and generally well tolerated. It improves the patient's bone mineral density and reduces the risk for low-trauma osteoporotic fractures. Given the fact that it is given once yearly, intravenously, it is an easy and convenient therapeutic option especially for older patients with polypharmacy who have adherence or tolerance problems with oral bisphosphonates. Its' efficacy and safety are well established in the literature and it continues to be a reliable and safe option, used as a first line treatment in post-menopausal osteoporosis.

KEYWORDS: Zoledronic acid; post-menopausal osteoporosis.

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue resulting in increased bone fragility and increased danger for fractures [1]. It is the most common metabolic bone disease in developed countries affecting more than 200 million people around the world [2]. It usually affects post-menopausal women and its prevalence increases with age. The most important clinical consequence of osteoporosis is the increased risk for fragility fractures. It is estimated that about 50% of women and 25% of men older than 50 years will suffer an osteoporosis-related fracture in their remaining lifetime [3].

The presence of osteoporotic fractures is associated with increased mortality and decreased quality of life, as many patients fail to return to their previous level of function after an osteoporotic fracture [4]. The high prevalence of the disease and the associated fractures also result in very high economic costs for healthcare systems. Additionally, due to

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the continuously growing number of the aging population around the world, the osteoporosis related fractures pose a great healthcare problem globally and their number is expected to continue to rise [5,6]. It is estimated that the number of people affected by osteoporosis will increase from 44 million to more than 61 million by 2020 in USA and the annual fractures and associated costs will increase by 50%. The worldwide incidence of hip fractures is estimated to be increased by 240% in women and 310% in men between 1990 and 2050 [7].

The clinical importance of post-menopausal osteoporosis.

The main problems caused by osteoporosis related fractures are morbidity, mortality and high health care cost. Therefore, the main goal of any therapeutic intervention is to reduce the incidence of osteoporotic fractures. An age-related decline in BMD can be seen in both men and women but the greater amount of loss happens in postmenopausal women. Age and gender are the two most important predisposing factors for the development of osteoporosis and the majority of patients suffering from this disease are postmenopausal women. The reasons for this are that women have a lower peak bone mass compared to men and also due to the hormonal changes happening after the menopause. Estrogens are very important in preserving bone mass in women and the gradual decline of these hormones after menopause results in increased bone absorption and decline in BMD. Osteoporosis is an asymptomatic disease, meaning that a patient can suffer from it while having few or no symptoms. The disease can exist and progress for years asymptomatically, until its clinical manifestation with skeletal deformities, skeletal pain and osteoporotic fractures. An osteoporotic fracture is defined as a fragility fracture caused after minor force, usually a fall.

The most common osteoporotic fractures are vertebral fractures. In some cases, small vertebral fractures can be asymptomatic but usually they cause great acute or chronic pain and spinal deformity, worsening the patient's quality of life and consisting a great source of morbidity [8]. These fractures usually happen after mild trauma or even simple daily activities like lifting objects or bending. Every fracture is correlated with higher risk for future fractures [9,10,11].

Another common type of osteoporotic fractures are hip fractures which almost always demand surgical intervention and are often considered life threatening conditions in elderly patients. Hip fractures dramatically reduce the patient's quality of life and are correlated with many post-surgery complications including decrease of functional capabilities and increased mortality [12,13]

Long term outcomes are often disappointing regarding patients return to their previous functional status as only one third of patients return to their pre-fracture functional level [14] The main goal of any therapeutic intervention is to reduce the risk for osteoporosis related fractures, mainly using anti-osteoporotic medication, calcium supplementation and lifestyle modifications targeting in fall prevention.

The absolute indications for anti-osteoporotic treatment in the elderly are well studied and documented and include the following categories.

- Patients with fragility fractures.
- Patients with a densitometric diagnosis of osteoporosis (T-score -2.5 or lower at the total hip, femoral neck, lumbar vertebrae, or distal one-third radius)
- Patients with osteopenia and a FRAX® score of >3% or >20% for hip and other major osteoporotic fractures, respectively.

Mode of Action of Zoledronic Acid

Bisphosphonates (BPs) are considered nowadays a first-line treatment against osteoporosis as it is a relatively safe, affordable and very effective category of drugs. The BPs have proven in multiple studies to be able to increase BMD and reduce the risk for osteoporotic fractures [15,16]. They act as anti-resorptives slowing down bone resorption and thus preventing the decrease of BMD. The BPs currently available in Europe are alendronate, risedronate, ibandronate and zoledronic acid. Once BPs

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TABLE 1 *Summarized effect of zoledronic acid on incidence of fractures.*

Study	Endpoint	Absolute reduction in fracture incidence %	Relative risk reduction in fracture incidence %	P value
HORIZON-PFT (Postmenopausal women)	**Vertebral fracture**			
	Over 12 months	2,2	60	<0,0001
	Over 24 months	5,5	71	<0,0001
	Over 36 months	7,6	70	<0,0001
	Hip fracture			
	Over 36 months	1,1	41	P = 0,0024
	Non-vertebral fractures			
	Over 36 months	2,7	25	<0,0001
	Hip fracture			
	Over 36 months	1,1	41	P = 0,0024
	Non-vertebral fractures			
	Over 36 months	2,7	25	<0,0001
HORIZON-RFT (Patients with hip fracture)	**Any clinical fracture**	5,3	35	<0,001
	Clinical vertebral fracture	2,1	46	0,02
	Non-vertebral fracture	3,1	27	0,03
	Hip fracture	1,5	30	0,18

are absorbed, they can be rapidly localized to the skeleton, where they inhibit bone resorption by reducing the creation and activity of osteoclasts and also increasing osteoclast apoptosis. The bisphosphonates mainly act by preventing further bone loss and are connected with minor increases in BMD. Aminobisphosphonates inhibit bone resorption by blocking the action of the enzyme farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway. This reduces osteoclastic bone resorp-

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tion through accumulation of unprenylated small guanosinetriphosphatases within the osteoclast. Bisphosphonates are stable analogues of pyrophosphate, but contain a carbon in the back bone of the molecule (P-C-P in bisphosphonate) instead of an oxygen (P-O-P in pyrophosphate) [17].

BPs have a strong affinity for bone hydroxyapatite. The addition of side chains of different lengths and structures allows many structural variations, producing BPs with a range of potencies and properties, which affects the clinical doses required. Like every other BP zoledronic acid has a high affinity for mineralized bone and binds to the calcium phosphate bone mineral hydroxyapatite mostly at sites with high bone turnover. When compared with alendronate, ibandronate, risedronate, etidronate, and clodronate, zoledronic acid has the highest affinity for hydroxyapatite in vitro [18].

Zoledronic acid has been proved to rapidly reduce the rate of bone turnover, by reducing both bone resorption and bone formation. This is demonstrated by the rapid and marked reduction of biochemical markers of bone resorption and bone formation after the beginning of treatment. These markers were more suppressed after the infusion of zoledronic acid, compared with placebo or weekly oral aledronate [19,20]. Their suppression reached their lower level at 7 days for the resorption markers and at 12 weeks for the formation markers. This well documented reduction at the rate of bone turnover and bone remodeling results in the antiresorptive properties of the drug.

Oral BPs are very effective, but also have important disadvantages. They are poorly absorbed, and are required to be taken on an empty stomach, with no food or drink for the next 30 minutes in order to maximize their absorption. Other disadvantages of the oral BPs are their gastrointestinal symptoms which are very often in the common clinical practice [21,22,23].

Zoledronic acid is a BP which is used once a year intravenously. Its usual dose is 5mg. It has been shown by multiple studies that its use reduces the risk of both hip and vertebral fractures. The fact that the drug is given via intravenous infusion is particularly useful in patients with gastrointestinal symptoms after oral BP administration as it allows to bypass the gastrointestinal system which also deals with the problem of poor gastrointestinal absorption. Its annual iv administration also overcomes the problem of poor patient compliance which is an often phenomenon in oral BPs administration.

Pharmacokinetic properties of Zoledronic acid

The exact pharmacokinetic properties of the drug have not yet been clarified, but it is known that its maximum plasma concentrations are achieved at the end of its infusion. After this, its concentration is rapidly decreased and reaches 1% of its maximal concentration 24 hours after the infusion. This rapid decrease of the levels of the drug in the plasma happens mainly for two reasons. First it is bound to bone very fast due to its high affinity for hydroxyapatite and secondly it is quickly excreted from the kidneys [24]. The drug cannot be metabolized in humans and a great amount of it, estimated about 39% is excreted intact in the urine by the kidneys , in the first 24 hours [24]. The amount of drug bound to the bones can remain there for years and can be released back to the plasma very slowly. The exact rate of release from the bone is not known but it can be detected in the urine even 8 years after the last treatment. Mild or moderate renal failure do not change its clearance compared to normal renal function and the drug can be used safely in these patients. Severe renal failure is the main contraindication for the drug as it is exclusively excreted by the kidneys and there are no data on its use in this population [25].

Therapeutic efficacy of Zoledronic acid

The largest and most important clinical trial considering the use of zoledronic acid for the treatment of postmenopausal osteoporosis was the HORIZON-Pivotal Fracture Trial. It included 7765 postmenopausal women, 65-89 years old which had a femoral neck T-score of -2.5 SD or lower with or without existing vertebral fractures or T-score -1.5 SD or lower and existing vertebral fractures. Patients randomly received 5mg zoledronic acid once a year (n=3889),

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or placebo (n=3876), at the beginning of the trial, 12 and 24 months after. Their follow up continued for three years. The trial proved that patients who underwent treatment with zoledronic acid experienced less vertebral, hip and other osteoporotic fractures and also less days of limited activity because of back pain or fractures, compared to those receiving placebo [26].

Zoledronic Acid and Vertebral fractures.

Vertebral fractures are some of the most usual types of fragility fractures, affecting millions of post-menopausal women. They can be identified either clinically or radiographically. Many new vertebral fractures are identified only radiographically as they are asymptomatic and do not become clinically apparent until multiple fractures occur.

The clinical importance and treatment options of these asymptomatic fractures is not clarified in the literature, nevertheless they are a frequent consequence of osteoporosis and most importantly a good predictor for subsequent fractures. Sustaining numerous vertebral fractures leads to clinically important outcomes, such as changes in height and posture which results in obstructed breathing, increased risk of fall, chronic pain, and functional limitations.

The HORIZON study indicated that there was a relative decrease of 70% in new vertebral fractures after treatment with zoledronic acid, compared with placebo. Regarding multiple vertebral fractures the same study showed a relative decrease of 89% in people treated with zoledronic acid , compared with placebo.

Zoledronic acid and Hip fractures

Hip fractures are considered the most important clinical outcome of osteoporosis because of the associated increase in morbidity and mortality. Many patients suffering a hip fracture are unable to return to their prior level of functioning and independence, resulting in substantial social and financial costs. Treatment with zoledronic acid has proved to be effective as it demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The absolute fracture rate was 1.4% after treatment with zoledronic acid versus 2.5% at the placebo group [26].

Zoledronic Acid and Non-vertebral fractures

The HORIZON study reported a reduction of the incidence of overall clinical fractures, including hip fractures. The absolute fracture rates in the zoledronic acid and placebo groups at 36 months were 8.4% and 12.8%, respectively, demonstrating a 4.4% absolute reduction in fracture incidence.

Zoledronic Acid and Risk for second fracture.

The Horizon study estimated the role of zoledronic acid in patients with established osteoporosis or osteopenia and existing vertebral fractures. The drug proved to be very effective, but the study did not consider secondary prevention of new fractures after a first hip fracture. This led to the design of a new phase 3 randomized controlled trial (RCT), the Horizon RFT (Recurrent Fracture Trial), in which 1065 male and female patients were randomized to receive a 5-mg infusion of ZOL and 1062 patients received a placebo infusion within 90 days after surgical repair of a hip fracture, with annual infusions of drug or placebo thereafter until the study end. As in the previous Horizon PFT, all patients received daily oral calcium (1000–1500 mg) and vitamin D (400–1200 IU). The result of the study after a follow-up of 22 months was a significant 35% reduction in any new clinical fracture (8.6% in the ZOL group and 13.9% in the placebo group) [27]. More specifically, any new clinical vertebral fractures (46%) and nonvertebral fractures (27%) were significantly reduced in patients who received zoledronic acid. However, although there was a reduction of second hip fractures in the ZOL group compared with placebo (30%), this did not reach statistical significance. Regarding the safety of this practice there was the expected significant increase in acute phase response (APR) reactions within 3 days of the first infusion in the ZOL group compared with placebo, but not after subsequent infusions. There was no difference in serious adverse events including atri-

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al fibrillation and stroke and during the follow-up there was a 28% reduction in deaths in the ZOL group compared with placebo.

Zoledronic Acid and BMD changes

In the HORIZON-PFT study the BMD was measured at the lumbar spine, femoral neck and total hip and the percentage of change before and after treatment was also used to estimate the efficacy of the treatment. It was proved that the treatment with zoledronic acid significantly increased BMD at the lumbar spine, total hip and femoral neck, relatively to treatment with placebo at time points 12, 24, and 36 months. Specifically it resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.1% at the femoral neck, over 3 years, compared to placebo.

Zolendronic Acid, Falls prevention and overall quality of life.

Another important aspect of osteoporotic fractures is the danger of fall. BMD is the main factor determining the risk for fracture but falls are the necessary aspect of almost every osteoporotic fracture. More than 90% of osteoporotic hip fractures result after falls. Some studies indicate that falls can have an equally important role as BMD in the pathogenesis of a fracture in the elderly [28].

Recent research indicated that except its already known therapeutic effects, zoledronic acid is connected with a reduced risk of falls. The balance ability and the fall risk before and after two years of treatment was calculated and the results indicated that the risk of falls was reduced at patients treated with zoledronic acid. It was also demonstrated in the same research that therapy was able to improve the overall health related quality of life [29].

Regarding the overall quality of life of osteoporotic patients , treated with zoledronic acid, there are little data, but they suggest that it is beneficial. In an analysis of the HORIZON-PFT trial, patients treated with zoledronic acid were shown to experience less days of limited activity caused by back pain or fracture, compared to those receiving a placebo [30]. It was also reported that treatment with zoledronic acid reduced the number of bed days related to a fracture [31].

Comparison of zoledronic acid with other anti-osteoporosis therapies

The anti-fracture effect of ZOL is impressive but it is hard to directly compare this with other osteoporosis therapies due to differences in study designs. The overall antifracture efficacy is impressive at both vertebral and nonvertebral sites and almost identical to the extremely potent antiresorptive therapy with denosumab. Compared with placebo, denosumab reduced vertebral, nonvertebral, and hip fractures by 68%, 20%, and 40% respectively [32]. These outcomes are very similar to those demonstrated in the HORIZON PFT. Regarding other bisphosphonates, ZOL in a single annual infusion was compared with weekly oral alendronate in women with osteoporosis. In a 24-week trial, 1 week after the first dose of both drugs, ZOL induced a greater reduction in the bone resorption markers urinary N-telopeptide of type I collagen and for serum β-C-telopeptide of type I collagen with the greater reduction continuing through the 24 weeks of observation [33].

In another comparator study, women who had already been taking alendronate for at least 12 months were randomized in a double-blind fashion to 70-mg weekly alendronate or a single infusion of 5 mg of ZOL and followed up for 12 months. The study concluded that there were only small increases in BMD from baseline in both groups and there was no superiority of either drug. This demonstrated that alendronate users could be effectively switched to ZOL but there was no specific benefit over simply continuing with alendronate therapy [34].

Complications related to treatment with Zoledronic Acid.

In general, treatment with zoledronic acid is safe and well tolerated by patients. Complications related with treatment are relatively rare and can be categorized in six main groups: acute phase reaction (APR), hypocalcemia, renal dysfunction, cardiovascular complications, eye inflammation, osteonecro-

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sis of the jaw and atypical subtrochanteric fractures. The commonest complications are acute phase reactions which resemble the symptoms of flu, like fever, headache, myalgia and arthralgia. These reactions usually happen the first three days after drug administration and symptoms usually resolve spontaneously without special treatment [35].

Acute phase reaction becomes apparent within 24-36 hours and consists mainly of fever and musculoskeletal pain. All symptoms considered as acute phase reaction present in the first 2 days after the drug infusion, with their incidence being rare after 3 days. The pathogenesis of these reactions is not fully understood but they are believed to be caused by release of inflammatory cytokines by T cells in the circulation [36].

The most important symptoms consisting the clinical condition of acute phase reaction are: fever, musculoskeletal (pain and joint swelling), gastrointestinal (abdominal pain, vomiting, diarrhea) and general symptoms (including fatigue, nasopharyngitis, edema). The most usual event is fever, which, together with non-specific symptoms such as chills and flushes, occur in about 20% of zoledronic acid-treated patient. About the same proportion of patients can suffer acute musculoskeletal symptoms, mainly pain, which is experienced as a generalized discomfort. Also, the patients can suffer from stiffness of the joints and muscles, and about 10% experience joint swelling. Another common complaint during acute phase reaction is symptoms from the gastrointestinal system. Nausea, vomiting, abdominal pain and diarrhea are the main complaints of patients. Regarding the severity of the symptoms, it was rated by patients as mild or moderate in more than 90% of the events [37].

The acute phase reaction does not pose a serious threat to the patient's health but in some cases, it can cause great discomfort to the patient or even results to absence from work and activity.

The presence of these reactions after a treatment can affect the patient's overall compliance to the anti-osteoporotic treatment plan, as patients can possibly avoid the next programmed drug administration being afraid of the recurrence of symptoms. The danger of acute phase reactions has been found to be reduced by the administration of acetaminophen or ibuprofen before injection of zoledronic acid and three days after that [38]. In general, most of the symptoms of acute phase reaction are easily managed with acetaminophen or NSAIDS.

The possibility of APR should be noted in order to gain informed consent from the patients. It is also important to inform the patient that the risk is for APR is greatly reduced on redosing. The above information is essential, as patients who have already experienced APR are usually very concerned about new APR after redosing.

In conclusion, the APR is by far the commonest side effect from the use of iv amino-bisphosphonates, and all patients should be informed about it. Despite its high incidence, it is usually of mild to moderate severity and lasts only a few days. For the above-mentioned reasons, it usually has minimal impact on long-term compliance to therapy. It is less common in patients who have previously used bisphosphonates. There is evidence that its severity can be reduced by half with co-administration of acetaminophen, so the short-term use of this drug is advised in patients receiving their first iv dose of an amino-bisphosphonate in order to lessen the risk of APR.

Hypocalcaemia is a complication that can occur after any BP treatment if the patient has calcium or Vitamin D deficiency and does not receive a rich in calcium diet or supplementation, as BPs drastically change bone metabolism. The use of calcium and Vitamin D supplementation is a common practice in every osteoporotic patient treated with BP, thus hypocalcaemia in these patients is extremely rare. As the hypocalcaemia can be preexisting before therapy and be rapidly deteriorated with its onset it is advised that all patients should be assessed regarding their calcium and vitamin D levels before initiating treatment with zoledronic acid. Preexisting low calcium levels is a contraindication for treatment with biphosphonates and should be corrected with calcium and vitamin D supplements before the onset of the treatment with zoledronic.

Renal complications are rare and of minor clinical

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importance in otherwise healthy patients. In general, all intravenous bisphosphonates are associated with infusion rate-dependent effects on renal function, such as minor increase in serum creatinine levels or urinary protein. Studies have shown that in long term use, creatinine clearance is not deteriorated and no renal function is affected after zoledronic acid treatment [39]. Serum creatinine monitoring and increased hydration are recommended before every dose infusion only in cancer patients, in which prolonged infusion times and dose reduction are used depending on the creatinine clearance rate. In otherwise healthy patients the use of iv zoledronic acid for the treatment of osteoporosis is only contraindicated if they have severe renal impairment (creatinine clearance<35 ml/min) [40].

Cardiovascular complications are extremely rare and the mechanism connecting them to BP treatment is not known. The HORIZON study found that incidence of atrial fibrillation was increased in patients receiving zoledronic acid treatment compared with the placebo group [26]. On the contrary these findings were not supported by other large epidemiology studies, which did not find increased risk of atrial fibrillation after BP treatment. Regarding the severity of this possible complication and the widespread use of BPs as a first line treatment for osteoporosis, the FDA reviewed all the clinical studies involving BPs and concluded in 2008, that across all studies there was not observed a clear association between overall bisphosphonate exposure and the rate of atrial fibrillation.

Inflammatory eye reactions have been associated with bisphosphonate use, in older research, particularly with iv infusions of pamidronate. In various studies a number of different diagnostic labels were used to describe these symptoms (conjunctivitis, episcleritis, panophthalmitis), and all these represent a similar syndrome. The most common signs of this rare complication are lid edema, conjunctival hyperemia, and chemosis, while common symptomatology includes pain, diplopia, and blurry vision. In the HORIZON study, only one case of iritis presented in the patients receiving ZA treatment, which was successfully treated, resulting in no further problems [41]. A review of the literature in 2012 found fourteen published case reports, regarding this complication [42]. Another more recent review found in 2015 that there was a total number of 29 cases in the literature [43]. The majority of cases (22/29, 76%) were associated with i.v. zoledronic acid infusion and the eye inflammation occurred the first month after infusion. The majority of patients underwent steroid treatment and the vision resolved in all patients except one case, in which anterior ischemic optic neuropathy occurred and caused permanent damage. Despite of its rare incidence, physicians should be aware for this possible complication.

Osteonecrosis of the jaw is probably the most notorious BP treatment complication as despite its extremely low frequency in healthy patients, it receives a great amount of interest from patients and also health care providers such as dentists. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) can be developed after treatment with both oral or intravenous BPs. This condition manifests as exposed non-vital bone in the maxillofacial area. The main event that triggers the development of this condition is trauma, usually after extended dental procedures. Trauma to the dentoalveolar structures becomes critical as they have a limited bone healing capacity due to the bisphosphonate therapy. The majority of patients developing BRONJ are cancer patients which are treated with high and frequent doses of intravenous BPs [44,45].

Other risk factors for ONJ except cancer and dental trauma, include duration of bisphosphonate exposure, sequential intravenous bisphosphonate therapy (pamidronate followed by ZOL), osteoarthritis or rheumatoid arthritis [46,47]. In 2014 the American Association of Oral and Maxillofacial Surgeons recommended changing the term BRONJ to medication-related osteonecrosis of the jaw (MRONJ), as other antiresorptive drugs, like denosumab have also been related to jaw osteonecrosis cases. Most studies indicate that the use of the recommended dose of 5mg of zoledronic acid once a year, for the treatment of postmenopausal osteoporosis does not affect the frequency of osteonecrosis of the jaw [48].

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Another study demonstrated that even if this problem can occur in up to 5% of bisphosphonate users with cancer of various varieties such as myeloma, it is extremely rare in those receiving lower doses for the management of osteoporosis, estimated as low as 1 in 100,000 [49]. In order to avoid this rare complication physicians can use simple preventive measures, such as screening of the patients dental hygiene and performing any invasive dental procedures before the onset of treatment.

Regarding the atypical subtrochanteric fractures, a number of recent case series have indicated that low trauma subtrochanteric hip fractures are increased in patients who are receiving BP treatment for many years [50,51,52,53,54]. Although the optimal duration of BP treatment is not clarified and the long-term use of BPs is relatively safe, this complication is of great importance for two reasons. First, osteoporosis is a chronic disease demanding long term therapeutic options, for often more than a decade and secondly this type of fracture poses an important complication affecting radically the patient's quality of life. Regarding the risks associated with this complication, in 2009, the American Society of Bone and Mineral Research (ASBMR) convened a multidisciplinary, international task force to clarify the risk of long-term BP therapy regarding atypical subtrochanteric fractures. The task force reviewed all research on this topic and concluded in 2010 that the incidence of atypical subtrochanteric fractures associated with BPs was very low particularly compared to the number of vertebral, hip and other fractures prevented by BPs. It concluded that a causal association between BPs and atypical subtrochanteric fractures could not be established [55].

Another review demonstrated that even if the relative risk of atypical subtrochanteric fractures is high in patients on BPs, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 patients [56]. Thus, these fractures are extremely rare, particularly compared against the incidence of common osteoporotic fractures of all types, which have been proven to decrease with BP therapy. Despite the rare possibility of atypical fractures, this scenario should be considered among patients receiving long BP therapy and reporting unexplained thigh pain.

Zoledronic acid, patients' compliance and cost-effectiveness

Despite the fact that osteoporotic fractures are one of the commonest reasons for hospitalization in the elderly, connected with high cost, morbidity and mortality, osteoporosis is often underdiagnosed and undertreated. Even when patients are diagnosed with osteoporosis, often after a first osteoporotic fracture, and antiresorptive treatment is started, a great number of patients discontinues therapy.

One important issue to consider is the patient's compliance with long-term intake of a medication for an essentially asymptomatic condition. Poor compliance is a well-documented and well-studied problem in these patients. The effectiveness of anti-osteoporosis treatment is greatly reduced because of poor patient adherence. Some research indicates that only 20% of women with osteoporotic fractures receive treatment, 50% do not take the treatment as prescribed, and 50% discontinue therapy after six months [57]. Another study indicated that only 50% of women with osteoporosis and multiple risk factors, receiving anti-osteoporosis treatment, perceived themselves to be at increased risk of fracture [58].

Some of the most usual reasons for poor adherence include poor patient education, a lack of patient understanding of their condition, patients concern about side effects, dosing intervals, polypharmacy, asymptomatic disease manifestation ('silent disease') and an overall underestimation of the risk for fracture. Poor patients adherence is associated with elevated fracture risk and this underlines the importance of compliance and persistence [59].

Oral BP treatment has a number of disadvantages compared to iv therapy which are responsible for the patient's poor compliance to therapy. BPs are poorly absorbed by the gastrointestinal system due to their large molecular structure,low lipophilicity and negative charge [60]. Less than 1% of oral

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bisphosphonates are absorbed when given per os. This very low bioavailability of orally administered bisphosphonates necessitates a very strict daily or weekly administration routine that often interferes with the patient's regular daily routine. The patient must take the oral bisphosphonate while fasting, with a glass of water, and must not eat, drink, take any other medication or lie down for 30 minutes, in order to increase their poor absorption and decrease the risk of gastro-esophageal reflux. These constraints have raised adherence issues [61,62].

Zoledronic acid is a therapy administered to patients intravenously on a yearly basis and this means greater compliance of patients and guaranteed absorption and bioavailability [63,64]. Patients seem to prefer these less frequent dosing regimens and intravenous (IV) infusion to the oral intake of bisphosphonates [65,66].

Conclusively, treatment of osteoporosis and especially postmenopausal osteoporosis with zoledronic acid is well-documented to increase BMD and reduce the risk for any osteoporotic fracture. It is relatively safe and well tolerated. Considering the fact that patient adherence to oral BPs is relatively low in terms of peptic disorders or frequent intake, the once a year treatment plan with ZA can provide an important and useful treatment option.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Η οστεοπόρωση αποτελεί την συχνότερη μεταβολική πάθηση των οστών και χαρακτηρίζεται από μειωμένη οστική πυκνότητα και ποιότητα με αποτέλεσμα τον αυξημένο καταγματικό κίνδυνο.Το ζολεδρονικό οξύ είναι ένα διφωσφονικό τρίτης γενιάς που χορηγείται ενδοφλέβια μια φορά τον χρόνο για την θεραπεία της οστεοπόρωσης και έχει αποδειχθεί πως είναι εξαιρετικά αποτελεσματικό και ασφαλές. Βελτιώνει την οστική πυκνότητα των ασθενών και μειώνει θεαματικά τον κίνδυνο για οστεοπορωτικά κατάγματα. Λόγω της ετήσιας ενδοφλέβιας χορήγησής του, είναι μια εύκολη και πρακτική θεραπευτική επιλογή, ειδικά σε ηλικιωμένους ασθενείς με πολυφαρμακία ή σε ασθενείς με πτωχή συμμόρφωση στα από του στόματος διφωσφονικά. Η αποτελεσματικότητα και η ασφάλειά του είναι καλά τεκμηριωμένες και εξακολουθεί να παραμένει μια αξιόπιστη και ασφαλής επιλογή ως θεραπεία πρώτης γραμμής για την μετεμμηνοπαυσιακή οστεοπόρωση.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Ζολεδρονικό οξύ, μετεμμηνοπαυσιακή οστεοπόρωση