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Research Article

Post-Menopause Osteoporosis: Oral or Venous Treatment?

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Abstract:

Patients with high risk of fragilty fractures, and those with recent fractures, should receive the highest priority for anti-osteoporotic treatment due to the severe consequences (morbidity and mortality of some of these fractures Chip, vertebrae, pelvis and humerus). The duration of treatment should be based on the assessment of fracture risk.

This work used as a methodology a literature review by searching the PubMED database between 2009 and 2019 with the keywords: "osteoporosis", "zoledronic acid", "alendronate sodiurn", "cost analysis effectiveness"," health economics ".

In this study, we can see that the most cost-effective postmenopausal anti-osteoporotic therapy should use oral Alendronate sodium or generic parenteral zoledronic acid. The choice of the ideal treatment should be based on the side effects of medications or by medication adherence. Considcnng the advantage of dosage convenience and treatment adherence with annual use of parenteral zoledronic acid, this drug may be a cost-effective treatment option compared with oral alendronate.

KEYWORDS: Cost-effectiveness analysis, Health economics, Osteoporosis, Zoledronic acid, Alendronate.

Introduction

Osteoporosis is the most common skeletal disease, caused by an imbalance in bone turnover, specifically a relatively increased rate of bone resorption by osteoclasts that exceeds the rate of bone formation by osteoblasts. Postmenopausal osteoporosis is the most common form of osteoporosis, affecting a significant proportion of women in the postmenopausal period and advancing with aging. Given that the life expectancy of women in Western countries is currently over 80 years and continues to rise, there is a gradual loss of bone mass and attenuation of bone strength over time, predisposing individuals to fractures from low-energy trauma (falls from standing height). Projections for women at risk of osteoporotic fractures in the coming decades, along with the associated economic burden on healthcare systems, are expected to rise continuously. (1)

Fall prevention is particularly important in the elderly or in individuals with fragile bones. Orthopedic or neurological disorders of the lower limbs are naturally contributors to falls. An ergonomic analysis of the home environment, with risk management adaptations for patients using antihypertensive and hypnotic medications, is essential. Consolidated data exist on the approach to these preventive measures (cataract surgeries reduce the risk of proximal femoral fractures by 16% compared to individuals with untreated cataracts). (2)

Osteoporotic fractures are associated with morbidity, pain, functional disability, and mortality. Standard prevention is typically considered through the use of oral bisphosphonates or parenteral medications, which are reserved for patients intolerant to oral medications. The decision to prescribe any of these medications depends on their effectiveness and side effects. There is also the responsibility to use these medications cost-effectively. Therefore, the need for anti-osteoporotic agents that can be administered for prolonged periods with effectiveness and safety is paramount. A common and effective treatment strategy in osteoporosis is targeting osteoclasts, thus reducing the rate of bone resorption. Anti-resorptive agents are currently the cornerstone of osteoporosis treatment. Bisphosphonates (BPs) have served as the primary agents in this category for several decades. Over the past decade, denosumab (DEN), a monoclonal antibody that binds to the receptor activator of nuclear factor-kappa B ligand (RANKL), inhibiting osteoclast formation and activity, has introduced a new category of more sophisticated biological agents targeting osteoclasts and initiated a new era in our efforts to treat the disease. DEN has gradually gained market share over BPs year after year, despite its significantly higher cost. The study evaluated summarizes the characteristics of these two commonly used anti-osteoporotic treatment modalities and the differences between them. Recent meticulous meta-analyses have reviewed the clinical picture, advantages of various currently approved medications (alendronate [ALN], risedronate [RIS], ibandronate [IBM], raloxifene [RLX], denosumab [DEN], teriparatide [TER], and zoledronic acid [ZOL]). Although the authors differentiate the type of fracture, the analyses do not emphasize the different clinical significance concerning morbidity or mortality of the fracture event. (3)

DEN acts similarly on osteoclast precursors, which is the natural receptor target of RANKL. DEN binds to RANKL, thereby preventing the binding of RANKL to its receptor, RANK, on osteoclasts and osteoclast precursors. Subsequently, the RANK signaling pathway is not activated, resulting in impaired differentiation of osteoclast precursors and their function, and potentially osteoclast apoptosis. All of these effects lead to the inhibition of bone resorption. Bisphosphonates (BPs) act on osteoclasts, but not on their precursors. BPs are internalized into osteoclasts, possibly through endocytosis. Subsequently, BPs inhibit farnesyl

pyrophosphate (FPP) synthase, a key enzyme in the mevalonate signaling pathway. This leads to the degradation of intracellular proteins and the accumulation of cytotoxic intermediate products, including APPPL, thereby impairing osteoclast function and potentially inducing osteoclast apoptosis. Thus, bone resorption is inhibited. (1) Fig. 1

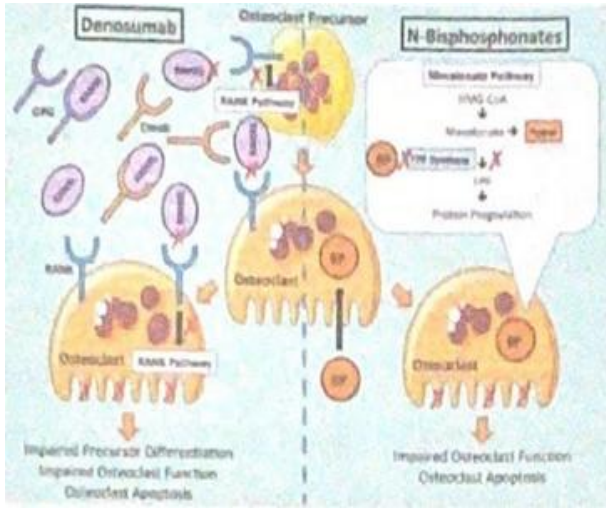

Fig. 1 - Summary of the different mechanisms of action of DEN and BPs. (1)

Furthermore, as prescribers, we must consider the cost relative to the benefit of fracture prevention. Therefore, we are committed in this study to re-evaluating existing meta-analyses and supplementing primary information as references to provide a path that may be more appropriate for the clinical decision-making process. Additionally, we question whether a fracture occurring during medical therapy should be considered a "treatment failure." Since none of the medications are 100% effective in fracture prevention, it is considered reasonable to account for the cost of switching from one class to an alternative class of medication after a fracture. We conducted a cost-effectiveness analysis of switching from an oral to a parenteral medication in the case of failure with oral therapy. (3)

Bisphosphonates (BPs) are the most commonly used medications for osteoporosis. Two trials provided evidence for the long-term use of BPs. In the Fracture Intervention Trial with Long-Term Extension (FLEX), postmenopausal women receiving alendronate for 10 years had fewer clinical vertebral fractures compared to those who switched to placebo after 5 years. In the HORIZON Extension, women who received 6 annual infusions of zoledronic acid (ZOL) had fewer morphometric vertebral fractures compared to those switched to placebo after 3 years. A low hip T-score, between -2 and -2.5 in FLEX and below -2.5 in the HORIZON Extension, predicted a beneficial response to continued therapy. Therefore, the studies suggest that after 5

years of oral treatment or 3 years of intravenous treatment, a reassessment of risk should be considered. In high-risk women, such as older women, those with a low T-score or high fracture risk score, those with a previous significant osteoporotic fracture or a fracture during therapy, continuing treatment for up to 10 years (oral) or 6 years (intravenous), with periodic evaluation, should be considered. The risk of atypical femoral fractures, but not jaw osteonecrosis, clearly increases with the duration of therapy, but such rare events are outweighed by the reduction in vertebral fracture risk in high-risk patients. For women without high fracture risk after 3 to 5 years of treatment, a drug holiday of 2 to 3 years may be considered. The suggested approach for long-term medication use is based on limited evidence, primarily for the reduction of vertebral fractures in postmenopausal women, mostly white, and does not replace the need for clinical judgment. It may be applicable to men and patients with glucocorticoid-induced osteoporosis, with some adaptations. (4)

**In the work by Briot et al. (2), it is observed that we should prioritize the treatment of two patient populations: first, patients who have already suffered a major fracture (such as fractures of the proximal femur (PF), proximal humerus, pelvis, and vertebrae); this notion of severity is based on the consequences of these fractures on mortality. Vertebral fractures that are "incidentally" discovered on radiographs should be considered as vertebral fractures with clinical expression. For other fractures, such as wrist fractures, the decision is more difficult and depends on the analysis of all other risk factors, particularly the results of bone densitometry.

Other patients who should be treated are those for whom the occurrence of a fracture could worsen their fragile state, such as individuals with respiratory failure (restrictive pulmonary disease related to thoracic fractures aggravating obstructive syndrome), Parkinson’s disease with repeated falls, etc. The management of patients after fractures is insufficient; the prescription of osteoporosis treatment after a proximal femur fracture has decreased by 50% in the last decade in the United States. In France, less than 20% of patients are treated after an osteoporotic fracture, and almost none are treated after a proximal femur fracture. More complex is the decision to treat individuals without fractures, with the goal of preventing primary fractures. In these cases, bone densitometry plays an essential role. The densitometric situation described as "osteoporosis" is defined by a T-score < -2.5. This T-score is relevant only at three measurement sites: lumbar spine, total hip, and femoral neck; other sites should not be considered. It should be remembered that the threshold of < -2.5 was chosen so that the prevalence of osteoporosis calculated this way in women over 50 years of age would be comparable to the lifetime risk of femoral neck fracture (17% and 15%, respectively). This threshold is not a therapeutic decision threshold.

The so-called "osteopenic" situation, that is, a T-score between -1 and -2.5, is not a bone disease but a

densitometric term that allows for epidemiological and clinical studies and should not be used in medical practice. Sensitivity and specificity for non-vertebral fractures based on bone density measurement are approximately 50-70%, which makes it impossible to identify all individuals who will experience a fracture based on this test. Bone density measurement alone cannot be used to make a therapeutic decision. It should be accompanied by an analysis of clinical risk factors for fractures, as proposed by the FRAX® tool and the analysis of fall risk.

The FRAX® tool provides the probability of a subject experiencing a fracture or major fractures, such as a proximal femur fracture, within 10 years. The FRAX® tool illustrates the impact of comorbidities on bone fragility: rheumatoid arthritis, for example, increases fracture risk independently of corticosteroid use. In the French recommendations, the therapeutic decision threshold based on the FRAX® calculation is equivalent to the probability of fracture recurrence based on age. - Fig. 2. The treatment recommendations, therefore, propose a pragmatic approach, starting with two questions: is there a history of fracture? Are there risk factors for osteoporosis or recurrent falls?

Fig. 2 - Therapeutic decision based on the individual fracture probability (FRAX®): French recommendations (2).

The probability of fractures and other adverse events in adults is demonstrated in the graph. - Fig. 3. The risk of fractures with BP therapy and of stroke with aspirin therapy is illustrated. The fracture incidence rates are age-standardized, while for other events, they represent crude rates in the United States. For atypical femoral fracture, the risks represent those reported during BP therapy for 5 and 10 years. (4)

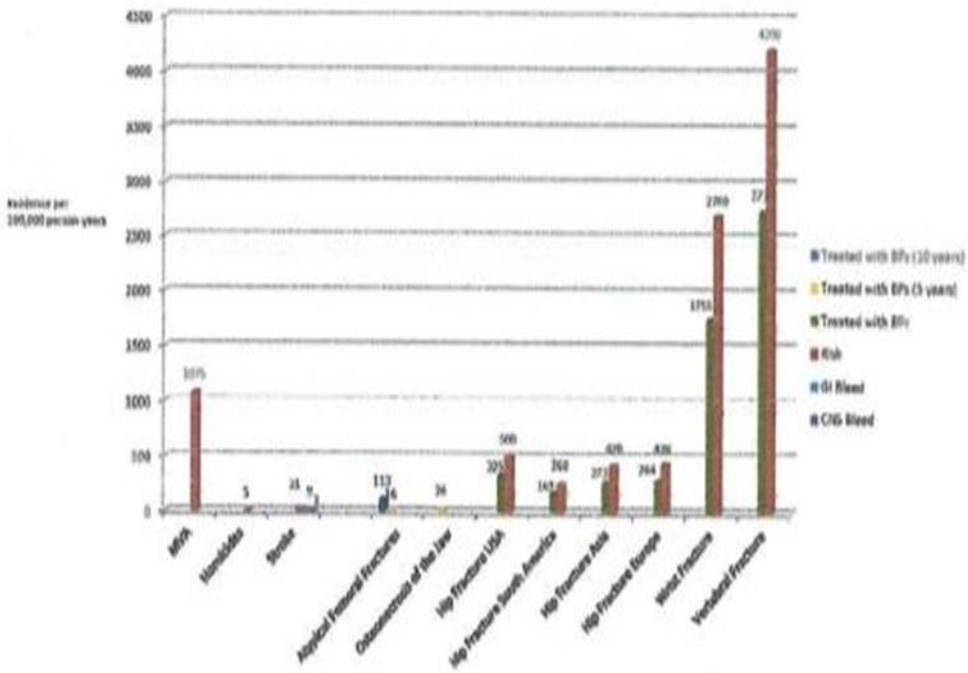

Fig. 3 - Risks associated with bisphosphonates and other health outcomes. (4)

Objective

The objectives of this study were to assess the cost-effectiveness of the use of medications (Sodium Alendronate and Zoledronic Acid) in the treatment of severe osteoporosis and to propose the standardization of the high-cost treatment (Zoledronic Acid) through usage guidelines (criteria for medication indication).

Methodology

A literature review was conducted through a search in the PubMED database between 2009 and 2019. The primary references included all randomized clinical trials of anti-osteoporotic medications and meta-analyses using the following search terms: "osteoporosis," "zoledronic acid," "sodium alendronate," "osteoporotic fracture," "cost-effectiveness analysis," "fracture prevention," and "health economics."

Results

Evaluating the results of the meta-analysis, studies were conducted in 43 randomized, placebo-controlled trials with double blinding, involving 71,809 postmenopausal women comparing fracture frequency. The

trials were similar in recruitment age, with a mean of 67.3 years (SD ± 8.1), and a follow-up time of 25.5 months (SD ± 12.6). Cost comparisons were evaluated for a treatment strategy assuming generic alendronate (ALN) as first-line therapy. Denosumab (DEN) and teriparatide (TER) showed benefits in reducing vertebral fractures over ALN, with incremental costs of $46,000 and $455,000 per fracture avoided, respectively. Zoledronic Acid (ZOL), recently launched as a generic, would be cheaper or comparable in cost. None of the alternative medications were statistically better in preventing hip fractures. TER was more effective in preventing non-vertebral fractures at an incremental cost of $1,555,000. (1)

In the results of a study on patients with osteopenia treated with ZOL administration every 18 months for 6 years, a reduction in the risk of fragility fractures (both vertebral and non-vertebral) was observed in older women with hip bone mineral density indicating osteopenia. The reduction in non-vertebral fracture risk was similar to that reported previously in patients with osteoporosis treated with ZOL (4). The results address an important knowledge gap identified in the recently published American College of Physicians guidelines on osteoporosis, which state that "current evidence is limited for a treatment benefit for women aged 65 and older with osteopenia," endorsing pharmaceutical treatment in this patient group. In contrast, the 2014 National Osteoporosis Foundation guidelines endorsed pharmacological intervention in women with osteopenia who had a 10-year hip fracture risk of over 3%, although the guideline noted that "there are relatively few data confirming fracture risk reductions with pharmacotherapy in this patient group." (5)

Symptoms resembling the flu (acute phase reaction) are suggested as an adverse event of Zoledronic Acid (ZOL); however, these symptoms are mild to moderate and are considered transient, disappearing within about 3 days. Adverse events associated with Alendronate (ALN) therapy were not considered because their impact on long-term costs and clinical benefits was relatively small. It can be assumed that patients on ZOL or ALN therapy who experience a secondary fracture will continue the preventive ZOL therapy or ALN therapy unless their status changes to a bedridden patient. (5)

The main adverse effects of anti-osteoporotic treatment include: gastrointestinal risk of oral bisphosphonates, potential neurotoxicity from intravenous bisphosphonates administration, and thromboembolic risk with raloxifene. Two other very rare complications have been described and have gained significant notoriety: osteonecrosis of the jaw and atypical fractures. It is justified to check the dental status before starting treatment. All dental and periodontal care should be performed in the general osteoporosis population, as the treatment of oral pathologies carries much higher risk than the treatment of osteoporosis. The first cases of atypical femoral fractures were described in 2007, and the diagnostic criteria were defined in 2012. The incidence is 32 cases per million patient-years. (2) The incidence increases with the duration of treatment,

from 2/100,000 cases/year for 2 years, to 78/100,000 cases/year after 8 years of use. The frequency of this event is very rare and has not been estimated in patients receiving denosumab (DEN) as prolonged treatment. The risk decreases by 70% in the year following the discontinuation of bisphosphonate therapy. Various hypotheses have been presented to explain this risk; these atypical fractures are found in a very rare disease, hypophosphatasia. This further supports the indication for systematic measurement of total alkaline phosphatase (to check for abnormally low levels) before starting anti-resorptive treatment in cases of bone fragility. (2)

Discussion

The response of this scientific paper should guide the treatment of postmenopausal women with severe osteoporosis, aiming to reduce morbidity and mortality rates.

Among osteoporotic fractures, hip fractures, in particular, impose not only a clinical burden on patients, worsening their quality of life (QoL) and health outcomes, but also a significant socioeconomic burden in terms of medical expenses for treatment as well as nursing care. The survival rates reported for patients who suffered a hip fracture—81%, 49%, and 26% at 1, 5, and 10 years, respectively—are lower than those for the general population. Moreover, a QoL score for patients in the year following a hip fracture was reduced by 11.5% compared to baseline.

Pharmacological therapy is considered an effective measure to address the burden caused by osteoporotic fractures, and a wide variety of options are available today. One of the main issues regarding osteoporosis is the low rate of patients receiving treatment. According to the study, the prescription rate of anti-osteoporotic medications in patients who suffered a hip fracture was 18.7%, while the rate in those who did not receive treatment was 53.3%, suggesting that the number of patients receiving treatment is insufficient (6).

An annual intravenous injection of Zoledronic Acid (ZOL) is suggested to facilitate long-term treatment for patients and to avoid the adverse effects caused by oral bisphosphonates, which require daily, weekly, or monthly dosing.

Although pharmacological therapy for osteoporosis definitely reduces the risk of fractures and anticipates a reduction in the total cost of treatment for osteoporotic fractures, there is a possibility of an increase in the overall medication cost. Recently, the cost- effectiveness of various pharmacological therapies for osteoporosis has been studied in developed countries, and the results are influencing decision-making in clinical practice as well as health policies. An economic health assessment of Zoledronic Acid (ZOL)

conducted in Finland, Norway, and the Netherlands by Akehurst et al. reported that ZOL is cost-effective when compared to basic treatment (placebo, calcium, and vitamin D) or other bisphosphonates (6).

These studies analyzed differ from the two phase 3 ZOL trials, in which dosing was done at intervals of 18 months, and the use of calcium supplementation was very low (approximately 2%). ZOL has sustained action duration, with bone remodeling markers still suppressed for nearly half of the 5 years following a single infusion. McClung et al. found that annual ZOL administration for 2 years had effects on bone mineral density and bone tumor markers that were nearly identical to the effect of a single initial dose(5). The observed reduction in fracture risk in the current study suggests that annual administration may be unnecessary for maximum efficacy in fracture prevention, and longer intervals between doses should be considered.

Calcium supplements act as weak anti-resorptive agents in the treatment of osteoporosis, and this effect is likely trivial when combined with ZOL, which exhibits much more potent effects.

The strengths highlighted in the studies include: well-powered design for the primary outcome, long duration, and high participant retention rates. In the placebo group, 11.5% of participants initiated bisphosphonate treatment (compared to 3.3% of ZOL participants), so the benefit estimates are conservative. The trial duration indicated that the intervention may be sustained over the long term in clinical practice. The study involved only women aged 65 years or older with femoral bone mineral density characterized as osteopenia, so the findings should not be extrapolated to younger women, men, or individuals with normal bone mineral density (5).

Current studies have shown that treatment with ZOL every 18 months, with minimal calcium supplementation, reduced the risk of fragility fractures (both vertebral and non-vertebral) over 6 years in elderly women with femoral bone mineral density characterized as osteopenia.

A persistent question remains in osteoporosis treatment regarding a comprehensive definition of inadequate response to therapy, including the timeframe and whether the term "treatment failure" should apply to individuals receiving osteoporosis treatment. A patient may be considered to have an inadequate response to therapy if they experience a fracture with a decrease in Bone Mineral Density (BMD) or two or more fractures. The role of bone remodeling markers and BMD measurements, in combination with the number of fractures, contributes to a comprehensive evaluation of the issue that the physician must consider in clinical decision- making.

Determining when osteoporosis treatment is suboptimal or inadequate remains a challenge. Therefore,

continuous evaluation of treatment efficacy, including considering changes in therapy, should be conducted throughout the course of treatment. No treatment completely eliminates the risk of fracture, and a single fracture in the absence of a decrease in BMD may not necessarily indicate an inadequate response to therapy. Unfortunately, it is impossible to unequivocally determine if a treatment is ideal. Clinical judgment is required to determine the optimal future therapy for patients who experience fractures while undergoing ongoing treatment.

In the FREEDOM study, individuals with a baseline vertebral fracture who experienced a subsequent fracture were at the highest risk for further fractures. In this high-risk subgroup, there was a significantly greater reduction in subsequent fracture rates in individuals who continued or switched to denosumab (DEN) therapy. This suggests that individuals at high risk for fractures are those who benefit most from continued treatment with DEN, likely due to their higher baseline fracture risk.

Studies with patients who discontinued the use of Denosumab (DEN) in the treatment of osteoporosis have shown that the vertebral fracture rate increased after discontinuation, reaching levels observed in untreated participants. The majority of participants who sustained a vertebral fracture after discontinuing DEN had multiple vertebral fractures, with a higher risk in participants with a previous vertebral fracture. Therefore, patients who discontinue DEN should quickly transition to an alternative anti-resorptive treatment.

The increased vertebral fracture risk following DEN discontinuation may be due to the increase in bone resorption within 3 months after missing a scheduled dose. Rapid increases in bone turnover volume after stopping DEN, combined with the observation of an increased vertebral fracture risk during a median follow-up of 0.5 and 0.2 years of freedom and extension, respectively, raise the possibility that missing a dose — or delaying a dose for several months — may place the patient at increased risk for vertebral fractures.

Regarding other fractures, no significant differences were found in non-vertebral fracture rates after discontinuing DEN or placebo. There does not seem to be an early increase in non-vertebral fractures, but a rise in multiple vertebral fractures after stopping DEN. It is possible that the increase in cortical bone mass after at least 2 years of DEN treatment undergoes little change immediately after discontinuation, compensating for the biomechanical effects of increased trabecular bone resorption, particularly when DEN is interrupted. In contrast, high bone turnover rates have greater adverse effects on the amount and microstructure of trabecular bone, which contributes significantly to the strength of vertebral bodies.

Bisphosphonates bind to the bone surface and recirculate in the local microenvironment for a long time after treatment cessation, explaining the persistent gains in Bone Mineral Density (BMD) and continued

reductions in bone resorption. Other treatments (e.g., Raloxifene, estrogen, and Teriparatide) improve bone mass and decrease fracture risk during treatment, but bone turnover returns to baseline effectiveness for fracture risk and is lost after treatment interruption. Therefore, if a reversible anti-resorptive treatment for osteoporosis is discontinued, a period of treatment with a bisphosphonate or the use of another anti-resorptive agent should be considered to preserve gains in BMD and reduce fracture risk. Patients who have received two or more doses and then discontinued DEN should transition quickly to another anti-resorptive therapy, especially in patients with a history of previous vertebral fractures.

According to the studies, there is no reason to routinely plan a drug holiday or cessation of therapy after a fixed period of use for a patient who is appropriately prescribed a bisphosphonate to reduce fracture risk (9). In the few studies designed to assess the persistence of the fracture risk reduction benefit after therapy cessation, they suggest that there is some persistence in this fracture risk reduction after cessation of therapy for ALN, RIS, and ZOL. However, the data for each bisphosphonate are quite specific to a particular period of use and a specific period of discontinuation. It is not the same for all three. In the case of ALN and ZOL, although it appears there is persistence in fracture risk reduction in some fracture risk categories after drug cessation, there is a further risk reduction in additional categories if the drug is continued. Due to the study design with RIS, it simply cannot say whether the risk reduction in any category is better if the drug is continued after any particular duration of therapy compared to its discontinuation. In the absence of data, one can speculate about the overall persistence of the effect with IBN. There is no data suggesting that the fracture risk reduction benefit stops after a certain period of use for any of the bisphosphonates during the periods in which they were studied. Finally, in terms of safety, the occurrence of adverse effects such as osteonecrosis of the jaw and atypical fractures are rare, even after 3 or more years of use. If the individual truly needs the drug, the risk of any of these complications is unlikely to exceed the potential benefit (9).

In January 2011, a "limitation of use" indication was added to the prescribing information for review by the Food and Drug Administration (FDA) for all bisphosphonates approved for the treatment of osteoporosis. The statement reads: "The safety and efficacy (name of the bisphosphonate inserted) for the treatment of osteoporosis are based on clinical data from 3 years of duration." The optimal duration of use was not determined in the study (9).

Although 3 to 4-year bisphosphonate trials have not identified consistent safety concerns, several safety issues have emerged from sources other than trials, including osteonecrosis of the jaw, esophageal ulcers, and, more recently, atypical femur fractures (10). While there is still significant uncertainty about the relationship between bisphosphonate use, the duration of use, and the risk of atypical fractures, it remains a

safety concern, particularly with long-term bisphosphonate therapy. To assess the effect of ZOL beyond 3 years, an extension of the HORIZON-PFT trial was conducted in which women on ZOL for 3 years were randomly assigned to receive either ZOL or placebo for an additional 3 years. The study's goals were to assess the efficacy and safety of 6 years of ZOL versus 3 years followed by cessation, and to estimate the effect of offset after discontinuation of treatment (10).

In the extension of the HORIZON-PFT study, results showed reduced health risks and a decreased incidence of fractures with the use of annual 5mg intravenous ZOL, administered over 3 years. This treatment demonstrated a reduction in the risk of vertebral, hip, and other non-vertebral fractures by increasing bone mineral density (BMD) and decreasing bone remodeling rates (10). These results, along with similar-duration trials for oral bisphosphonates, support fracture risk reduction with 3 to 4 years of bisphosphonate administration, particularly in osteoporotic women. However, the efficacy of bisphosphonates in longer periods has been much less studied. The authors recommended that many women could take a drug holiday after 5 years of continuous treatment, but those at high risk for vertebral fractures should continue. A later post hoc analysis suggested benefits for non- vertebral fractures in those with lower BMD T-scores (below -2.5) after 5 years of treatment. This long-lasting effect is not true for all bisphosphonates; for example, one year after the discontinuation of RIS, there was no difference between the active and placebo groups in bone turnover markers (though BMD remained higher and fracture incidence stayed reduced in the active group) (10).

For treatment up to 10 years with oral bisphosphonates (FLEX extension) and 6 years with intravenous bisphosphonates (HORIZON extension), benefit and risk estimates are based on much weaker data. For patients who sustain fractures during therapy, adherence should be evaluated, and secondary causes of osteoporosis should be explored. Based on the FLEX and HORIZON extension studies, Caucasian women with fracture risk defined by advanced age (70-75 years) among other factors, re- evaluation should include a clinical assessment, risk evaluation, including analysis of risk factors, and may include bone mineral density measurement by Dual-Energy X-ray Absorptiometry (DXA). The monitoring interval with DXA should be based on detectible and clinically significant changes. Re-evaluation may be necessary in less than 2 years for patients with a new fracture or accelerated bone loss (e.g., in patients using aromatase inhibitors or glucocorticoid therapy) (4).

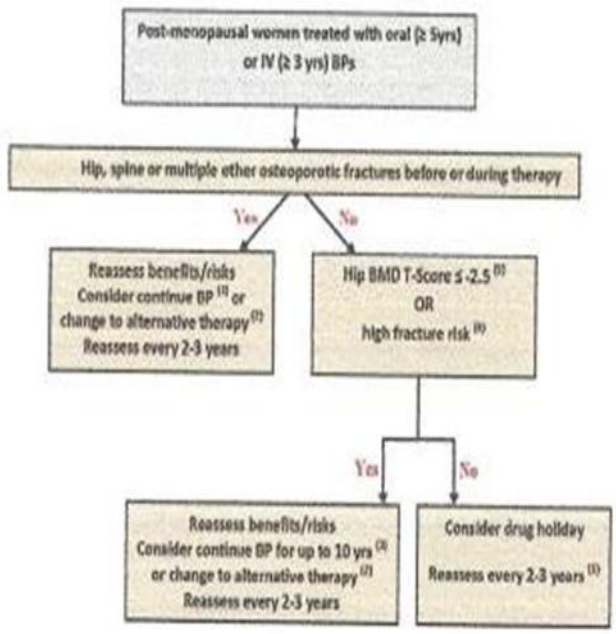

Fig. 4 - Approach to the management of postmenopausal women on long-term bisphosphonate therapy – The benefits of years of therapy clearly outweigh the risks.

Conclusion

The most effective initial therapy for reducing the costs of postmenopausal osteoporosis is the use of generic sodium alendronate (ALN) or zoledronic acid (ZOL) via parenteral administration. There is no statistically significant difference in the efficacy of available drugs to prevent hip fractures. There is limited data to suggest switching medications after sustaining an osteoporotic fracture during ALN therapy, although generic ZOL may be considered based on side effects or medication adherence issues. Considering the advantage of annual ZOL treatment compliance and persistence, this drug may be a cost-effective treatment option compared to ALN.

All patients on bisphosphonate therapy should have their continued need for therapy reassessed at a baseline period. Based on current knowledge, an automatic Drug Holiday or discontinuation of therapy should not be recommended for all patients treated with any bisphosphonate. Each patient should have this need reassessed at a baseline period, considering the patient's preferences and always adapting to evolving scientific updates.

If a therapeutic decision was made for a patient with low bone mineral density (BMD), it is desirable to have an increase in that density. In fact, the final bone mineral density value at the end of treatment is the only

determinant of fracture risk in the following years. Therefore, a T-score > -2.5 at the hip at the end of the first therapeutic sequence is a relevant therapeutic goal.

The fracture risk confidence intervals demonstrate that clinical recommendations should primarily be based on bone mineral density (BMD) markers, bone turnover, and the fracture risk threshold values. It is observed that the continuation of annual ZOL treatment for more than 6 years maintained BMD and reduced the risk of vertebral fractures.

Although discontinuation after 3 years showed an increase in morphometric vertebral fractures, there was also substantial evidence of residual benefits. These residual benefits after discontinuation suggest that after 3 years, many patients may interrupt infusions for up to 3 years, thereby reducing costs and potential adverse effects while maintaining efficacy. However, women at high risk of fractures, particularly vertebral fractures, may benefit from continuous annual infusions.

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