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Review article

Treatment of postmenopausal osteoporosis: a literature-based algorithm for use in the public health care system

Ellen Luz Pereira Caires[a], *Mailze Campos Bezerra*[b,c], *Ana Flávia Torquato de Araújo Junqueira*[a,c], *Sheila Márcia de Araújo Fontenele*[b,c], *Silvana Cristina de Albuquerque Andrade*[c,d], *Catarina Brasil d'Alva*[a,c,*]

[a] *Universidade Federal do Ceará (UFC), Faculdade de Medicina, Serviço de Endocrinologia e Diabetes, Fortaleza, CE, Brazil*
[b] *Universidade Federal do Ceará (UFC), Faculdade de Medicina, Serviço de Reumatologia, Fortaleza, CE, Brazil*
[c] *Universidade Federal do Ceará (UFC), Faculdade de Medicina, Núcleo de Atendimento Multidisciplinar às Doenças Osteometabólicas, Fortaleza, CE, Brazil*
[d] *Universidade Federal do Ceará (UFC), Faculdade de Medicina, Serviço de Nefrologia e Transplante Renal, Fortaleza, CE, Brazil*

ARTICLE INFO

Article history:
Received 3 July 2016
Accepted 5 December 2016
Available online 15 February 2017

Keywords:
Osteoporosis treatment
Bisphosphonates
Public health care

ABSTRACT

Bisphosphonates are considered first-line agents in the treatment of postmenopausal osteoporosis based on extensive experience of use, safety, and proven efficacy in reducing vertebral, non-vertebral and femur fractures. However, post-marketing reports based on the treatment of millions of patients/year over lengthy periods of time have revealed the occurrence of initially unexpected adverse effects, such as osteonecrosis of the jaw and atypical femoral fracture, leading to the restriction of treatment duration with bisphosphonates by global regulatory agencies. However, despite the association between these effects and bisphosphonates, this risk should be analyzed in the context of osteoporosis treatment, alongside the benefit of preventing osteoporotic fractures and their clinical consequences. Therefore, we consider it plausible to discuss the restriction to the use of bisphosphonates, possible indications for prolonged treatment and alternative therapies following the suspension of this drug class for patients with persistent high risk of fracture after initial treatment, especially considering the problems of public health funding in Brazil and the shortage of drugs provided by the government. Thus, to standardize the treatment of osteoporosis in the public health care system, we aim to develop a proposal for a scientifically-based pharmacological treatment for postmenopausal osteoporosis, establishing criteria for indication and allowing the rational use of each pharmacological agent. We discuss the duration of the initial bisphosphonate treatment, the therapeutic options for refractory patients and potential indications of other classes of drugs as first-choice treatment in the sphere of public health, in which assessing risk and cost effectiveness is a priority.

* *Corresponding author.*
E-mails: cbdalva@terra.com.br, majaco@terra.com.br (C.B. d'Alva).
http://dx.doi.org/10.1016/j.rbre.2017.01.001

Tratamento da osteoporose pós-menopáusica: um algoritmo baseado na literatura para uso no sistema público de saúde

Palavras-chave:
Tratamento da osteoporose
Bisfosfonatos
Saúde pública

RESUMO

Com base na vasta experiência de uso, segurança e eficácia comprovada na redução de fraturas vertebrais, não vertebrais e femorais, os bisfosfonatos são considerados agentes de primeira linha no tratamento da osteoporose pós-menopáusica. No entanto, os relatos pós-venda baseados no tratamento de milhões de pacientes/ano durante períodos prolongados de tempo revelaram a ocorrência de efeitos adversos inicialmente inesperados, como osteonecrose da mandíbula e fratura atípica do fêmur. Isso levou as agências reguladoras globais a restringirem a duração do tratamento com bisfosfonatos. No entanto, apesar da associação entre esses efeitos e os bisfosfonatos, esse risco deve ser analisado no contexto do tratamento da osteoporose, paralelamente ao benefício na prevenção de fraturas osteoporóticas e suas consequências clínicas. Portanto, considera-se plausível discutir a restrição ao uso dos bisfosfonatos, possíveis indicações para o tratamento prolongado e terapias opcionais após a suspensão dessa classe de fármaco para pacientes com alto risco persistente de fratura após o tratamento inicial, especialmente se considerarmos os problemas financeiros de saúde pública no Brasil e a escassez de fármacos fornecidos pelo governo. Assim, para padronizar o tratamento da osteoporose no sistema público de saúde pretende-se desenvolver uma proposta de tratamento farmacológico cientificamente fundamentada para a osteoporose pós-menopáusica, estabelecer critérios de indicação e permitir o uso racional de cada agente farmacológico. Discutem-se a duração do tratamento inicial com bisfosfonatos, as opções terapêuticas para pacientes refratários e potenciais indicações de outras classes de medicamentos como tratamento de primeira linha na esfera da saúde pública, em que a avaliação do risco e custo-efetividade é uma prioridade.

Introduction

Osteoporosis is characterized by loss of bone mass and deterioration of tissue microarchitecture, leading to bone fragility and increased risk of fractures, the clinical consequences of which are deformities, chronic pain, disability and death.[1] It is a common disease with increasing prevalence among men and women due to increased life expectancy and an aging population.

Bisphosphonates represent the first-line therapy for the prevention of osteoporotic fractures.[2] These drugs are synthetic analogs of inorganic pyrophosphate obtained by replacing the oxygen atom with a carbon (P-C-P), making them resistant to biological degradation, and by adding two side chains (R1 and R2), responsible for skeletal binding affinity and power, respectively. This chemical structure has the property of forming compounds with divalent cations, showing great avidity with hydroxyapatite crystals of bone surfaces, particularly of active remodeling sites. In the acid environment of resorption, bisphosphonates are released from the bone and absorbed by the osteoclast, causing the inhibition of the enzyme farnesyl pyrophosphate synthase, which is important for the integrity of its cytoskeleton and cell function. This leads to a loss in resorptive function and potential osteoclast apoptosis. Considering that bone formation and resorption are coupled processes, reduced resorption is followed by a decrease in bone formation, thus achieving a new state of decreased bone remodeling after starting the treatment.[3]

The first drug of this class was synthesized in the 19th century, but its clinical relevance was only recognized in the late 1960s, when bisphosphonates started being used in the treatment of various bone metabolic diseases.[4] However, the widespread use of bisphosphonates in osteoporosis therapy occurred after 1993, when World Health Organization (WHO) established the diagnosis of osteoporosis by the technique of bone densitometry by dual-energy X-ray absorptiometry (DEXA).[5]

Effectiveness of bisphosphonates in the prevention of osteoporotic fractures

Alendronate, risedronate, ibandronate and zoledronic acid are the bisphosphonates currently approved for the treatment of osteoporosis. The anti-fracture efficacy of these drugs has been established by large population studies.[6–9] Initially, Liberman et al.,[6] in a phase III study ($n = 994$ women, age 45–80 years, lumbar spine T-score ≤ -2.5, 3-year follow-up), showed a 48% reduction in the risk of radiographic vertebral fractures with use of alendronate, which was approved for treatment of osteoporosis in the US in 1995. The first major study designed to evaluate the effect of this drug on the risk of vertebral and non-vertebral fractures was the Fracture Interventional Trial (FIT, $n = 2027$ women with previous vertebral fractures, age

55–81 years, neck T-score ≤ -2.1, 2.9-year follow-up), which showed a reduction of 47%, 55% and 51% in the risk of radiographic vertebral fractures, clinical vertebral fractures and femur fractures, respectively, in this group of postmenopausal women with previous vertebral fractures.[7]

The second bisphosphonate approved for the treatment of osteoporosis in the US was risedronate, in 2000. The use of risedronate (VERT study, $n = 2458$ women, age <85 years, 2 prior vertebral fractures or 1 prior vertebral fracture plus spine T-score ≤ -2.0, 3-year follow-up) resulted in 41% and 39% reductions in vertebral and non-vertebral fractures, respectively.[9] Then, a 40% reduction of hip fracture risk was shown by McLung et al. in a large study that included 5445 women aged 70–79, with neck T-score ≤ -4.0 or neck T-score ≤ -3.0 plus 1 risk factor for hip fracture, in a two-year follow-up.[10]

Ibandronate, approved in 2005 for the treatment of osteoporosis, reduced the risk of vertebral fracture by 62% (BONE study, $n = 2946$ women, age 55–80 years, T-score ≤ -2.0 in at least one vertebra plus prior vertebral fracture, 3-year follow-up). In this study, there was no reduction in the risk of non-vertebral fractures, except for a post hoc analysis of the subgroup of women with neck T-score < -3.0.[11] In order to estimate the effect on non-vertebral fractures, a few meta-analyzes of randomized studies that evaluated individual patient data were published suggesting a beneficial effect of higher doses of ibandronate (corresponding to 150 mg/month orally or 12 mg/year i.v.).[12,13] However, there is no evidence from placebo-controlled studies showing a reduced risk of non-vertebral fracture with the use of ibandronate.

Zoledronic acid, a bisphosphonate with greater antiresorptive potency, was approved for the treatment of osteoporosis in 2007. An annual infusion of zoledronic acid for 3 consecutive years (HORIZON PFT, $n = 7765$ women, age 65–89 years, neck T-score ≤ -2.5 or neck T-score ≤ -1.5 plus 1 vertebral fracture, 3-year follow-up) was effective in reducing by 70%, 41% and 25% the risk of vertebral, femur and non-vertebral fractures, respectively.[14]

Safety of bisphosphonates in osteoporosis treatment

Given that osteoporosis is a chronic disease, along with the good safety profile of bisphosphonates demonstrated by placebo-controlled studies, osteoporosis treatment should, conceptually, be extended throughout the patient's whole life. However, post-marketing reports based on the treatment of millions of patients/year over a lengthy period of time revealed the occurrence of initially unexpected adverse effects of bisphosphonate treatment such as osteonecrosis of the jaw (ONJ) and atypical femoral fracture.[15–17]

ONJ is characterized by exposure of bone tissue in the maxillofacial region without healing after 8 weeks.[18] Evidence suggests the existence of a causal relationship between the use of bisphosphonates and ONJ, with a dose-response effect due to the greater incidence of this complication in cancer patients receiving high cumulative doses of bisphosphonates. The prevalence was estimated at 0.4% among cancer patients and 0.001% in patients with osteoporosis in a survey of cases observed by Canadian maxillofacial surgeons.[19] A randomized, double-blind, placebo-controlled study involving 2046 patients with breast cancer observed the occurrence of ONJ in 2.0% and 1.4% of those treated with high doses of denosumab or zoledronic acid, respectively ($p = 0.39$), revealing that this effect is not specific to bisphosphonates, but to treatment with potent antiresorptives.[20] Therefore, ONJ is very rare in the treatment of osteoporosis and discontinuation of antiresorptive therapy in osteoporotic patients prior to dental procedures possibly does not have any impact in reducing this risk.

However, recently, the Task Force on ONJ recommended to stop antiresorptive therapy, if it is possible to do so without adverse consequences for bone health, in patients who require extensive invasive oral surgery as well as those with multiple risk factors for ONJ, although there is little evidence to support this recommendation as bisphosphonates remain in bone for years.[21] Therefore, clinical judgment is always essential.

A further complication observed following the marketing of bisphosphonates was atypical femoral fracture defined as noncomminuted transverse or short oblique fractures, which occur in the subtrochanteric region after minimal trauma.[22] Despite the inconclusive studies on bone physical properties in bisphosphonates users, it is believed that such fractures are the result of excessive and prolonged suppression of remodeling, causing loss of bone quality and mechanical function, which leads to the accumulation of microfractures and skeletal fragility. The result is the development of insufficiency fractures at the maximum mechanical overload point represented by the subtrochanteric or diaphyseal region of the femur. Hence the term atypical fracture, since it involves the strongest region of the femur, unlike osteoporotic fracture, which commonly occurs in the femoral neck.[23]

After reviewing 12,777 femur fractures cases that occurred in Sweden in 2008, Schilcher et al.[24] identified 59 atypical fractures, 78% of which occurred in bisphosphonates users. Despite this association, the absolute risk of atypical fracture related to the use of bisphosphonates is low (50 cases/100,000 patients-year). Dell et al.[25] analyzed approximately 15,000 subtrochanteric fractures in California between 2007 and 2009, identifying 102 atypical fractures, 97 of which in patients using bisphosphonates for an average of 5.5 years. However, when analyzing the use of bisphosphonates over time, the absolute risk was 2 cases/100,000 patients-year in 2 years of treatment and 78 cases/100,000 patients-year in 8 years of treatment.

Warnings from drug regulatory agencies worldwide

A report issued by the Brazilian Agência Nacional de Vigilância Sanitária (ANVISA) in 2013 warned prescribers about long-term safety issues of bisphosphonates and recommended to stop therapy after three years, analyzing for each individual patient whether the use of this class of drugs for more than 3 years is necessary and justifiable.[26] This warns concurs with reports issued by the Food and Drug Administration (FDA) in 2010 and by the European Medicines Agency (EMA) in 2011.[27,28]

Impact of the regulatory restriction on duration of bisphosphonates use in the Brazilian public health system: a critical analysis

Despite the association demonstrated between atypical femoral fractures and bisphosphonates, this risk should be analyzed in the context of osteoporosis treatment, alongside the benefit of preventing osteoporotic fractures. It is estimated that for each 100 typical femoral fractures prevented by bisphosphonates, 1 atypical fracture occurs.[29] For patients with severe osteoporosis and high risk of fracture, 3300 osteoporotic fractures are prevented per 100,000 patients-year treated, while for patients with moderate risk, 1700 osteoporotic fractures are prevented per 100,000 patients-year treated with bisphosphonates.[22] Therefore, the effectiveness of this class of drugs in the prevention of osteoporotic fractures in patients with moderate to high risk osteoporosis outweighs the risk of atypical fractures (Fig. 1).[30]

In Brazil, where the constitution guarantees universal access to health care, only raloxifene and alendronate are regularly available in our public health system. In order to obtain drugs such as zoledronic acid and teriparatide, patients turn to the courts, obliging the government to provide the medications, which disrupts its budget and impairs health policies. Thus, it is reasonable to question the restriction on the use of bisphosphonates, especially when we consider public health funding problems in Brazil and the scarcity of drugs supplied by the government.

Therefore, given the potential severity of osteoporosis, the absolute low risk of atypical fracture and the restricted drug supply by our public health system, it is reasonable to propose long-term bisphosphonates treatment for women with osteoporosis and moderate to high risk of fracture.

With the objective of standardizing the treatment of osteoporosis in Brazilian public health care system, as well as reducing the phenomenon of judicialization of health, we propose to develop a scientifically-based protocol for the treatment of postmenopausal osteoporosis, establishing criteria for indication and allowing the rational use of each pharmacological agent.

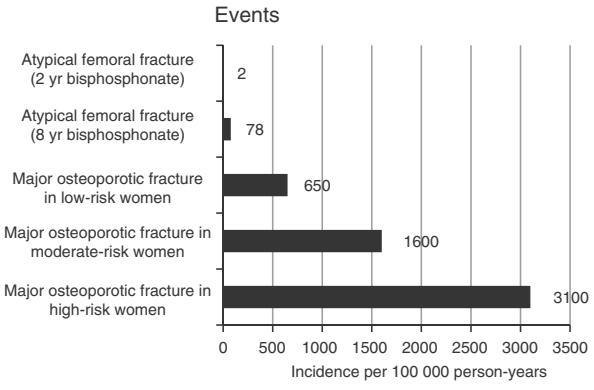

Fig. 1 – Risk of osteoporotic fractures and atypical femoral fractures.
Adapted from Brown et al.[30]

Efficacy of prolonged treatment with bisphosphonates

It is worth examining whether prolonged use of bisphosphonates offers benefits, since these drugs accumulate in the skeleton and continue to be released for months to years after the treatment is suspended, resulting in a residual anti-fracture effect.[31] Below are described some extension studies of treatment with bisphosphonates.

The extension of the FIT study (Fracture Interventional Trial Long-term Extension, FLEX), in which, following the first 5 years with alendronate, patients in the treated group were randomized into 5 more years of alendronate or placebo, showed no difference in the risk of non-vertebral fracture and morphometric vertebral fractures between the groups. However, it demonstrated a reduced risk of clinically apparent vertebral fractures (RR: 0.45; 95%CI 0.24–0.85) in patients continuing treatment for 10 years.[32] It is noteworthy that, in the FLEX study, many women had osteopenia only, and those with a femur neck T-score < -3.5 were excluded, indicating that part of them already presented low risk and had no need to prolong treatment. Moreover, a subsequent analysis of FLEX data showed that maintenance of alendronate for 10 years in the subgroup of women with a femoral neck T-score ≤ -2.5 decreased by 50% the risk of non-vertebral fractures (RR: 0.50, CI 95% 0.26–0.96).[33] These results indicate that some women, especially those with high risk of fracture, can benefit from the maintenance of treatment with alendronate for 10 years. In other words, the effectiveness of the prolonged treatment depends on the fracture risk, which can be evaluated, among other aspects, by Bone Mineral Density (BMD).

To investigate the long-term effects of zoledronic acid, patients who had been treated for 3 years in the HORIZON study were randomized into 3 more years of zoledronic acid or placebo. This study showed a reduction in the risk of morphometric vertebral fractures (OR: 0.51; $p = 0.035$) with continued treatment. This finding led to the conclusion that many patients can safely discontinue the medication after the initial 3 years of treatment, while some of them may benefit from the maintenance of zoledronic acid for another 3 years.[34]

We can conclude that suspension of the bisphosphonate after 3 (zoledronic acid) to 5 years (alendronate) is justified for patients who, at the end of this period, present low risk of fracture. However, those who persist with femoral T-score ≤ -2.5 after the initial course of treatment should have this treatment continued for up to 6 (zoledronic acid) to 10 years (alendronate). Moreover, despite the absence of evidence-based recommendations, it is likely that women who persist with moderate to high risk of fractures due to factors independent of femoral T-score may also benefit from treatment maintenance.

Transition studies: what to do in the case of women who persist with high risk of fracture following 10 years of treatment with bisphosphonates?

Some women persist with severe osteoporosis and high risk of fracture even after this prolonged treatment with

bisphosphonates, becoming candidates for treatment with other anti-osteoporotic drugs. However, bisphosphonates are potent suppressors of bone remodeling and have high affinity and retention time in the bone, inhibiting turnover for years after their suspension. Therefore, the impact of the switch to other drugs must be carefully analyzed.[35,36]

Given the greater potency of the zoledronic acid, McLung et al.[37] studied the effect of a single dose of this drug in menopausal women previously treated with alendronate for an average time of 4 years ($n = 225$, age 46–79 years, spine or neck T-score ≤ -2.0). BMD remained essentially stable after 12 months of alendronate or zoledronic acid, with no difference between the groups.

Denosumab, the first biological drug approved for the treatment of osteoporosis, is a monoclonal antibody that binds to receptor activator of nuclear factor kappa β ligand (RANKL), a cytokine secreted by the osteoblast considered essential for the differentiation, activity and survival of osteoclasts, potently reducing bone resorption and the risk of vertebral (68%), non-vertebral (20%) and femur (40%) fracture.[38,39]

Two studies investigated the effects of denosumab in patients previously treated with bisphosphonates.[40,41] Kendler et al.,[40] analyzing patients treated with alendronate for an average of 36 months ($n = 504$, age ≥ 55 years, $-4.0 \leq T$-score ≥ -2.0), observed that the transition to denosumab resulted in a significantly greater increase of BMD in the total femur and lumbar spine after 12 months compared to the maintenance of alendronate (1.9% vs. 1.0% total femur, $p < 0.0001$; 3.0% vs. 1.8% lumbar spine, $p < 0.0001$).

In patients using alendronate irregularly for a median of 20 months ($n = 870$, age ≥ 55 years), there was a significantly greater increase in BMD at all bone sites following the transition to denosumab compared with the transition to risedronate (total femur 2.0% vs. 0.5%, neck 1.4% vs. 0%; spine 3.4% vs. 1.1%, $p < 0.0001$ at all sites).[41]

Denosumab and bisphosphonates are both antiresorptive drugs, but have different mechanisms of action. They decrease osteoclast activity and survival, but RANKL inhibition by denosumab also prevents the differentiation of these cells.[42] Furthermore, it is possible that bone formation in a resorption-independent process, known as bone-modeling, persists at a lesser extent in adult skeletons and is preserved during denosumab treatment, as it was recently demonstrated in cynomolgus monkeys treated with denosumab.[43] Detection of endocortical and periosteal surface fluorochrome labeling reflected continued bone formation at specific sites, outside the trabecular compartment, providing preclinical evidence for a potential mechanism that could contribute to the effects of denosumab in BMD and fracture risk.[43] The different mechanism of action may be responsible for the further increase in bone mass caused by denosumab in previous bisphosphonate users.[40]

However, when BMD was analyzed according to the length of prior alendronate use, a greater increase in BMD with denosumab was observed in groups with shorter alendronate treatment duration, which can be explained by the filling of the bone remodeling units during the previous antiresorptive treatment.[40] This hypothesis can also explain the greater BMD gain with teriparatide in treatment-naïve patients.[40]

In this context, it is worth noting that these authors studied the effect of denosumab in women receiving bisphosphonates for a maximum period of 4 years, while, in our proposal, we intend to justify the use of other drugs after 10 years of bisphosphonates, which we suggest as a therapeutic strategy for our public health reality. Given the lack of transitional studies after such a long therapeutic course with bisphosphonates, it is our assumption that the switch to another antiresorptive drug might not offer any additional benefit in this particular circumstance.

Unlike the antiresorptive drugs discussed above, teriparatide, the 1-34 N-terminal fragment of parathyroid hormone (PTH), is an anabolic agent (inducer of osteoblast bone formation) whose intermittent administration results in the increase in the number and activity of osteoblasts, causing rapid bone mass increase and improved trabecular and cortical architecture.[44] It is the only class of anabolic drugs currently used in the treatment of osteoporosis. It causes a significant reduction in the risk of vertebral (RR: 0.35; CI 95% 0.22–0.55) and non-vertebral (RR: 0.47; CI 95% 0.25–0.88) fractures in menopausal women with prior vertebral fractures ($n = 1637$), although reduction of femur fracture has not been demonstrated so far.[45,46]

An important question is whether the prior antiresorptive treatment modifies the anabolic response to teriparatide. The benefits of teriparatide in patients previously exposed to antiresorptive drugs over long periods of time were tested by some authors.[47–52]

Ettinger et al.[47] studied the effect of 18 months of teriparatide in women previously treated with raloxifene or alendronate for a period of 18–36 months (EUROFORS study, $n = 59$, age 60–87 years, T-score ≤ -2.0). Both groups showed a statistically significant increase in bone turnover markers (BTM) (P1NP, bone FA and osteocalcin) as early as the end of the first month of teriparatide, with a tendency for further increase in the group previously treated with raloxifene. BMD increase occurred earlier in raloxifene users, but by the end of treatment BMD increase in the lumbar spine was observed in both groups, a gain of 10.2% for previous users of raloxifene and of 4.1% for previous users of alendronate ($p < 0.001$). However, BMD increase in total femur was significant only in previous users of raloxifene (0.5% in previous raloxifene users and – 1.8% in previous alendronate users, $p = 0.002$). The authors concluded that teriparatide stimulates bone turnover in women previously treated with raloxifene or alendronate for 18–36 months, although previous exposure to alendronate slows skeletal response to teriparatide. This delayed effect on BMD and more limited response after prior use of bisphosphonates is probably due to the absence of target cells for the anabolic effect of teriparatide. After few years of treatment with a potent antiresorptive, the extremely low bone turnover reduces the availability of pre-osteoblasts, osteoblasts and lining cells to be converted into osteoblasts.[35,48]

Investigating the risk of fractures during treatment with teriparatide in women previously treated with bisphosphonates for an average of 36 months (EFOS study, $n = 1581$), Jakob et al.[49] observed a progressive reduction of this risk analyzed by 6-month intervals, which remained evident even after suspension of teriparatide (37% reduction in fractures during 12–18 months of teriparatide and 76% during 12–18 months

following its suspension, compared to the initial 6 months of this treatment).

In addition, clinical studies examining bone mass by histomorphometry, high-resolution peripheral quantitative computed tomography (HR-pQCT) and finite element analysis in HR-pQCT showed that the suppressive effect of bisphosphonates may be offset by continued treatment with teriparatide.[50–52]

In short, these studies show effective anabolic response to teriparatide after previous treatment with bisphosphonates for an average period of 36 months. Again, there is no evidence of the use of teriparatide following more prolonged treatment with bisphosphonates, as we propose in our therapeutic strategy. There may be greater delay and more limited response of BTM and BMD, and clinical trials are needed to evaluate this therapeutic scenario. However, given the available evidence, we consider it acceptable to use drugs with anabolic effect in previous users of antiresorptives over a prolonged time span that, after such treatment, persist with severe osteoporosis and high risk of fracture.

Protocol for pharmacological treatment of postmenopausal osteoporosis in the public health care system

Alendronate as first-line treatment

Due to the extensive experience of use, safety and antifracture efficacy, bisphosphonates are the mainstay of osteoporosis treatment and should generally be used as drugs of first choice (Fig. 2). Considering the availability of alendronate in the Brazilian public health service, most patients with an indication of pharmacological treatment should receive alendronate, a priori for a period of five years, according to the presented evidence.

During treatment, no randomized study assessed the value of serial bone densitometry on the risk of fracture, but this test can be useful if used correctly.[53] Therefore, treatment monitoring by sequential BMD assessment is indicated, with bone mass stability and absence of new fractures in major bone sites as indicators of therapeutic success.[54] In addition, demonstration of a cross-link telopeptide of type 1 collagen (CTx) decline of 25% from baseline levels after 3–6 months of treatment can be used as early evidence of inhibition of bone resorption and good therapeutic response.[53,54]

Following the first 5 years of treatment, stopping alendronate therapy is suitable for most patients and a drug holiday should be considered with reassessment of fracture risk after 2 or 3 years. However, women with a femoral *T*-score ≤ -2.5 should have this treatment continued, considering the evidence of benefit in this subgroup of women by FLEX study.[33] Another important consideration is whether the patient had experienced previous osteoporotic fractures, especially in major bone sites. Since such fractures increase substantially future fracture risk, these patients should also have bisphosphonate treatment continued. It is worth considering that the benefit outweighs the risk of atypical femoral fractures in these groups of individuals, as well as the great impact of an osteoporotic fracture on mortality, quality of life and costs to the health system.[55] During this prolonged treatment period, drug suspension should be determined by the periodic assessment of the individual risk of fragility fractures.

After 10 years using alendronate, the risk of osteoporotic fracture should be reassessed. In view of the absence of evidence for fracture reduction and safety beyond such a long-term therapy, maintenance of bisphosphonate may not be appropriate. Then, in lower-risk patients, a drug holiday

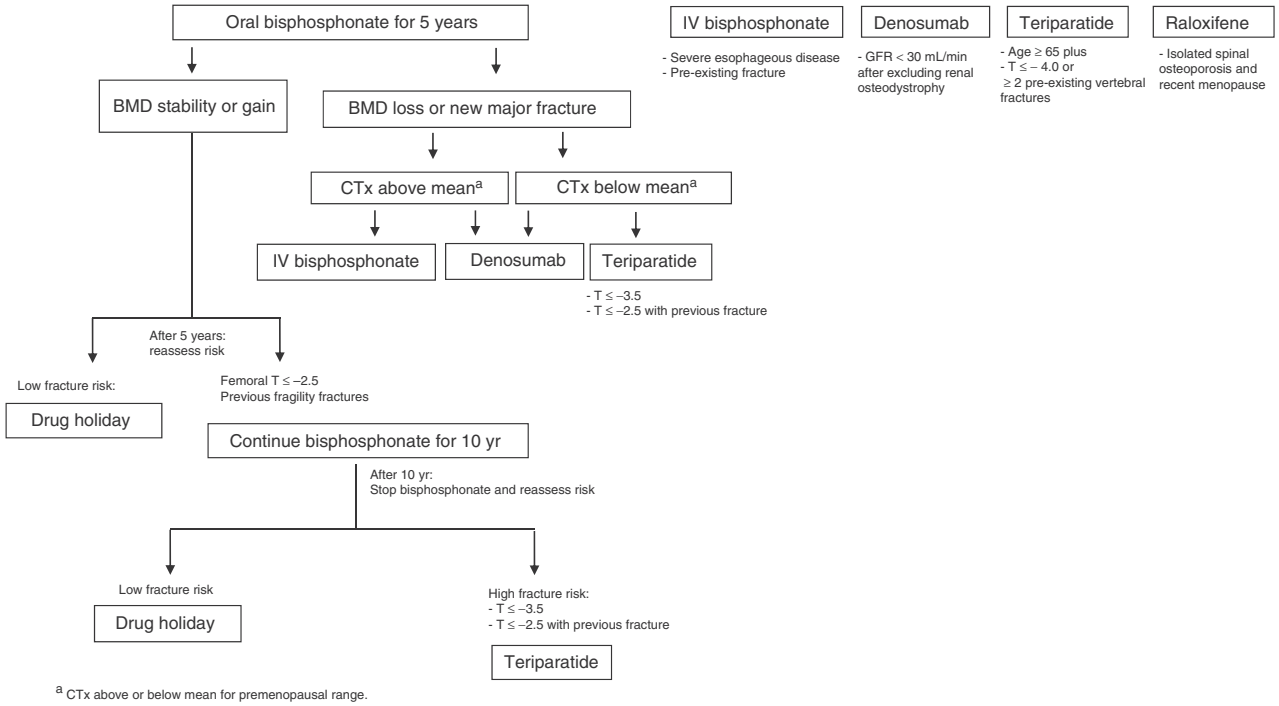

Fig. 2 – Proposal for pharmacological treatment of postmenopausal osteoporosis in the Brazilian public health care system.

should be considered and alendronate discontinued. However, for the non-negligible percentage of women with persistent high risk of fragility fractures, stopping osteoporosis treatment is not advisable. The options are to continue treatment with alendronate or switch to another anti-fracture medication. At this point, we propose a drug with anabolic mechanism of action for these high-risk patients with persisting severe osteoporosis, although there have not been studies evaluating efficacy of such an approach. The only anabolic drug available in the Brazilian market is teriparatide, approved for the treatment length of 24 months. Because of its high cost and limited evidence after such a prolonged antiresorptive treatment, we suggest selecting for its use only the subgroup of women with severe osteoporosis and higher risk.

The definition of severe osteoporosis by WHO includes pre-existing fragility fractures in the presence of T-score ≤ -2.5. The risk of a new vertebral fracture is five times higher in patients with prior vertebral fractures.[56] Moreover, considering BMD as an important determinant of fracture risk, high risk can also be arbitrarily defined as $T \leq -3.5$ score, even in the absence of fractures.[46]

Patients refractory to treatment with alendronate

Some patients are considered refractory to the treatment with alendronate, which must be verified by a decline in BMD in at least two serial BMD measurements or occurrence of new fragility fractures in main bone sites.[54] In such cases, review of compliance and a search for occult secondary causes of osteoporosis are mandatory. If adherence cannot be improved and secondary osteoporosis is excluded, switching to an alternative therapy is indicated.[54]

Most clinical practice guidelines have not recommended the measurement of BTM in the management of osteoporosis largely because they demonstrate high degrees of pre-analytical and analytical variability.[57] However, they provide a surrogate measure of the rate of bone turnover and there is growing evidence that they are potentially useful in determining fracture risk and response to therapy.[57] There is no reference to support their measurement to assess fracture risk after long-term bisphosphonate, but this is not the case. Considering the wide range of quality of available bisphosphonate formulations as well as the poor adherence to treatment, serum CTx levels may help to identify patients with high bone turnover, in whom bisphosphonate is not exerting its effects. Therefore, during bisphosphonate treatment, a CTx drop lower than 25% from baseline or, in the absence of pre-treatment values, a CTx above the mean of the pre-menopausal reference interval are indicative of active bone reabsorption.[54,58] Therefore, in this case of treatment failure along with CTx exceeding the lower half of premenopausal range, the transition to other anti-resorptive drugs, zoledronic acid or denosumab, would be indicated due to full absorption and greater anti-resorptive effect.

For patients who fail to alendronate despite adequately suppressed CTx, we believe that zoledronic acid might not offer benefit based on its absence of superiority on BMD in women with postmenopausal osteoporosis previously treated with alendronate, although this effect was demonstrated regardless of CTx.[37] Therefore, in patients with treatment failure along with adequately suppressed CTx, we infer that denosumab and teriparatide may represent the most appropriate agents. Once again, because of the high cost of teriparatide, the most severe subgroup of women with T-score ≤ -3.5 or T-score ≤ -2.5 with previous fractures would also have an indication for teriparatide.[46]

Although it is impractical to obtain CTx levels routinely in the public health system, we consider its measurement specifically in cases of treatment failure may help clinician in the decision of alternative therapy.

Use of other drugs as first choice

Finally, indication of other drugs as first-line treatment should also be considered in some clinical settings.

Zoledronic acid, owing to its great efficacy in reducing vertebral, non-vertebral and femoral fractures, as well as for its ease of administration and guaranteed absorption, can be the drug of choice in all scenarios where bisphosphonates are indicated. However, due to its unavailability in the public health system, we can arbitrarily reserve it for patients with contraindication for oral bisphosphonates, patients with more severe esophageal disease or those with prior fractures for having a higher risk of new fractures. It is estimated that adherence to treatment with oral bisphosphonates is lower than 40% in 1 year.[59]

Denosumab is the only drug indicated for the treatment of osteoporosis in patients with creatinine clearance <30 mL/min. However, the characterization of osteoporosis in patients with chronic kidney disease is complex, requiring the exclusion of renal osteodystrophy through laboratory tests and often bone histomorphometry.

Raloxifene, a selective estrogen receptor modulator with antiresorptive mechanism of action, discretely increases BMD and reduces by 30% the risk of vertebral fractures, not acting on non-vertebral and femur fractures.[60] Due to its lower efficacy in reducing fractures, we suggest its use in women with isolated spinal osteoporosis, in perimenopausal age.

Finally, given the fast improvement in bone mass and architecture seen in response to teriparatide, this drug could be indicated as first-line therapy in individuals at particularly high-risk for fractures, which includes the same more severe subgroup of women with T-score ≤ -3.5 or T-score ≤ -2.5 with pre-existing fractures.

However, it should be noted that there is an intersection in the indications of teriparatide and zoledronic acid as first-line agents in this proposal, concerning to women with pre-existing osteoporotic fractures. So, considering that the benefit of teriparatide in reducing the risks of vertebral and nonvertebral fractures was best demonstrated in women over 65 years with prevalent vertebral fractures,[45] as well as considering the greater risk attributed to aging, we advocate its use as first-line therapy for this group of patients over age 65 with at least two pre-existing vertebral fractures, in view of its much higher cost. Regarding to the other suggested indication of teriparatide for women with very low BMD in the absence of pre-existing fractures, we believe that the risk of an inadequate response to antiresorptive therapy is high when the skeletal architecture is too severely disrupted and the remodeling spaces are scarce.[61] Once more, because of teriparatide

high cost, we arbitrarily relocate its use as initial therapy in the group of women with very low BMD without previous fractures to those with *T*-score ≤ −4.0.

Conclusion

In conclusion, alendronate is an appropriate first-line drug to be used for a period of five years, with recommended extension for patients with persistent femoral *T*-score ≤ −2.5 and for those with previous fragility fractures. After 10 years of bisphosphonate treatment, there have not been clinical studies evaluating different approaches. At this time, a drug with anabolic mechanism of action may be appropriate for the high-risk patients with persistent severe osteoporosis. Furthermore, drugs as denosumab, zoledronic acid and teriparatide are options in cases of refractoriness to oral bisphosphonates as well as first-line therapy in specific clinical settings.

It is important to mention that currently, in view of the limited evidence, we do not have answers to many of our clinical questions, but we take advantage of the best scientific knowledge available to propose criteria for the rational use of pharmacological treatment of postmenopausal osteoporosis in the sphere of public health.

Conflicts of interest

The authors declare no conflict of interest.

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