REV BRAS REUMATOL. 2017;xxx(xx):xxx–xxx

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

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 xxx

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-mail: cbdalva@terra.com.br (C.B. d'Alva).

http://dx.doi.org/10.1016/j.rbre.2017.01.001

Please cite this article in press as: Caires EL, et al. Treatment of postmenopausal osteoporosis: a literature-based algorithm for use in the public health care system. Rev Bras Reumatol. 2017. 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
Bifosfonatos
Saúde pública

RESUMO

Com base na vasta experiência de uso, segurança e eficácia comprovada na redução de fraturas vertebrais, não vertebrais e femorais, os bifosfonatos são considerados agentes de primeira linha no tratamento da osteoporose pós-menopáusica. No entanto, os relatos pós-comercialização 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. Isto levou as agências reguladoras globais a restringirem a duração do tratamento com bifosfonatos. No entanto, apesar da associação entre estes efeitos e os bifosfonatos, este 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 bifosfonatos, possíveis indicações para o tratamento prolongado e terapias alternativas após a suspensão desta classe de fármaco para pacientes com alto risco persistente de fratura após o tratamento inicial, especialmente considerando 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, estabelecendo critérios de indicação e permitindo o uso racional de cada agente farmacológico. Discute-se a duração do tratamento inicial com bifosfonatos, 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

Please cite this article in press as: Caires EL, et al. Treatment of postmenopausal osteoporosis: a literature-based algorithm for use in the public health care system. Rev Bras Reumatol. 2017. http://dx.doi.org/10.1016/j.rbre.2017.01.001