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Review

Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review

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ABSTRACT

Introduction: Osteoporosis is a progressive skeletal disorder that requires long-term treatment. However, there is little guidance regarding optimal treatment duration and what the treatment discontinuation and retreatment criteria should be. Given that bisphosphonates are the most commonly prescribed class of agent for the treatment of osteoporosis, we reviewed the long-term data relating to these therapies and discussed the considerations for using bisphosphonates in postmenopausal women with osteoporosis.

Methods: A PubMed search, using the search terms 'bisphosphonate', 'postmenopausal osteoporosis' and 'long term' and/or 'extension' was conducted in January 2013. Results from nine controlled studies that prospectively assessed alendronate, risedronate, ibandronate or zoledronic acid in women with postmenopausal osteoporosis were reviewed.

Findings: Clinical studies in postmenopausal women with osteoporosis showed that long-term use of bisphosphonates resulted in persistent antifracture and bone mineral density (BMD) increasing effects beyond 3 years of treatment. No unexpected adverse events were identified in these studies and the long-term tolerability profiles of bisphosphonates remain favorable. Data from the withdrawal extension studies of alendronate and zoledronic acid also showed that residual fracture benefits were seen in patients who discontinued treatment for 3 to 5 years after an initial 3- to 5-year treatment period. BMD monitoring and fracture risk assessments should be conducted regularly to determine whether treatment could be stopped or should be reinitiated. Patients exhibiting T-scores < -2.5 or who have suffered a new fracture while on treatment should continue treatment, while patients with T-scores > -2.5 could be considered for discontinuation of active treatment while undergoing continued monitoring of their bone health. The duration and potential discontinuation of treatment should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities.

Contents

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Introduction

Osteoporosis is the most common bone disease in humans and affects both men and women [1]. It is a progressive skeletal disorder characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fracture [2]. In particular, hip fractures constitute the most serious of all osteoporotic fractures; they are associated with increased morbidity and mortality, and decreased ambulation, and are responsible for direct and indirect lifetime costs in excess of $20 billion in the United States of America (estimated cost in 1997) [3], and over £2 billion in the United Kingdom (in 2012) [4]. The burden of osteoporotic hip fractures increases with age. In the recently published Global Longitudinal study of Osteoporosis in Women, the proportion of incident hip fractures among incident major fractures increased more than five-fold with age, from 6.6% among women 55 to 59 years of age to 34% among those ≥85 years of age [5,6].

Current pharmacologic therapies for osteoporosis aim to prevent fractures through inhibition of bone resorption as well as stimulation of formation [7]. Although all the licensed therapies have demonstrated fracture risk reduction and/or increased bone mineral density (BMD) in clinical trials of postmenopausal osteoporosis, these studies were often no longer than 3 to 4 years in duration [8–12]. Owing to the chronic nature of osteoporosis and the fact that the burden of fracture increases with age, long-term fracture prevention is needed and treatment beyond 3 years may be required for the majority of patients.

Using anti-osteoporotic therapies for long-term treatment necessitates a number of considerations such as: Do all patients require long-term treatment? Which patients benefit most from long-term therapy? What is the long-term efficacy of licensed therapies? Who may discontinue treatment and what should the retreatment criteria be? Are there any potential safety concerns with chronic use of these agents?

A recent review by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis and the International Osteoporosis Foundation summarized the long-term fracture efficacy and safety data of currently available anti-osteoporotic agents [13], but new data have emerged since its publication. Given that bisphosphonates are one of the most commonly prescribed classes of agent for osteoporosis [14,15], this article reviews the latest long-term data relating to bisphosphonate therapy for the management of osteoporosis, and discusses the results in light of the aforementioned considerations for long-term use. The data presented pertain to the use of bisphosphonates in women, as no comparable data are available for men.

Methods

A PubMed search using the search terms 'bisphosphonate', 'postmenopausal osteoporosis', and 'long term' or 'extension' was conducted in January 2013. The search results were restricted to clinical trials only with no time limit. A total of 107 articles were retrieved from the search. Only controlled studies that prospectively assessed the use of alendronate, risedronate, ibandronate or zoledronic acid in women with postmenopausal osteoporosis are included in this review. Studies with a duration of ≤3 years, those that had bone histology or drug adherence as the main study end points, and those which involved <100 patients, assessed conditions other than postmenopausal osteoporosis, or focused on the use of non-bisphosphonates are excluded. Thus, data from 9 primary articles are reviewed in this paper. No formal meta-analysis of the retrieved articles was carried out because of the heterogeneity of the populations, interventions, lengths of follow up and drugs tested in the trials.

Long-term efficacy and safety of bisphosphonates

Long-term efficacy of bisphosphonates

Bisphosphonates are antiresorptive agents that decrease bone turnover by inhibiting osteoclast function. They are commonly used for the prevention or treatment of osteoporosis in women and, in some cases, in men. The bisphosphonate therapies currently licensed to treat postmenopausal osteoporosis include alendronate, risedronate, ibandronate and zoledronic acid. These drugs exhibit different degrees of potency for inhibition of the key enzyme in the mevalonate pathway, farnesyl phosphate phosphatase, and different affinities for hydroxyapatite binding sites on bony surfaces [16]. Bisphosphonates are available as oral formulations (alendronate, risedronate and ibandronate) for daily, weekly or monthly dosing, or as intravenous formulations for bimonthly or quarterly (ibandronate) or yearly (zoledronic acid) administration. These characteristics may contribute to differences in drug metabolism, compliance and, subsequently, risk reduction estimates among the bisphosphonates that are currently available [17–23]. However, no prospective head-to head studies have been conducted to assess whether these differences are reflected in real life variations among drugs in efficacy or safety.

Bisphosphonates have been studied in clinical trials of at least 3 years in duration with fractures assessed as the primary end point [8,9,12,24–27]. The registration trials of alendronate, risedronate and zoledronic acid were subsequently extended to investigate the long-term effects of these drugs (Fig. 1) [6,28–30]. Long-term studies of ibandronate were also carried out but these were performed as extensions of the non-placebo-controlled, non-inferiority studies that assessed either oral or intravenous ibandronate dosing regimens [31–34]. Owing to the size of these extension studies, BMD was assessed as the primary outcome measure with fractures often assessed as exploratory endpoints or as adverse events.

Fracture risk reduction with long-term bisphosphonate treatment

Alendronate. The 5-year, randomized, double-blind Fracture Intervention Trial (FIT) Long-term Extension (FLEX) study of alendronate included postmenopausal women with osteoporosis who had received an average of 5 years of alendronate therapy during and after FIT [28]. The FLEX study compared the effect of approximately 10 years of continuous alendronate treatment (n = 662; mean age, 72.7–72.9 years) with cessation of therapy (n = 437; mean age, 73.7 years) after 5 years of initial treatment. Fracture incidence was assessed as an exploratory endpoint and was based on adverse event reporting. The study found a significantly lower risk of clinical vertebral fracture among those who continued (pooled results of the 5 and 10 mg arms) versus those who stopped alendronate treatment (2.4% vs. 5.3%; relative risk, 0.45; 95% confidence interval [CI], 0.24–0.85; Fig. 2). However, discontinuation did not appear to increase the risk of nonvertebral or morphometric