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Monthly Risedronate for the Treatment of Postmenopausal Osteoporosis

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Abstract

Risedronate is a first-line medicine for the treatment of postmenopausal osteoporosis, since meta-analyses of large randomized controlled trials have demonstrated its efficacy against vertebral, nonvertebral, and hip fractures. Risedronate has desirable pharmacological characteristics in terms of its low affinity for bone, and its strong inhibition of farnesyl pyrophosphate synthase rapidly reduces bone turnoverand reverses the effect. Monthly risedronate, which has been recently approved, is non-inferior to daily risedronate in terms of changes in surrogate markers and the incidence of adverse effects. However, the incidence of acute phase reactions is higher for a monthly dosing regimen than for a daily dosing regimen. Because monthly bisphosphonates are superior to weekly bisphosphonates in terms of patient preference and convenience and, consequently, treatment adherence (particularly persistence), monthly risedronate is considered to be useful in clinical practice.

Keywords: Risedronate; Postmenopausal women; Acute phase reaction; Osteonecrosis of the jaw; Atypical femoral fracture

Introduction

Osteoporosis mostly affects postmenopausal women and substantially increases their risk of fracture. Fractures associated with osteoporosis (fragility fractures) have a major impact on quality of life, mortality, and health care costs. Therefore, it is important to prevent fragility fractures in patients with postmenopausal osteoporosis. The ideal osteoporosis treatment is a drug therapy with the efficacy against vertebral, nonvertebral, and hip fractures, good tolerability, good patient adherence, and low cost.

Oral bisphosphonates are the mainstay of treatment in most patients with postmenopausal osteoporosis. Bisphosphonates normalize bone turnover and increase bone mineral density (BMD), thereby preventing fragility fractures [1]. Risedronate (5 mg/day) was approved by the US Food and Drug Administration for the treatment of postmenopausal osteoporosis. Risedronate is a first-line medicine for the treatment of postmenopausal osteoporosis, since meta-analyses of large randomized controlled trials (RCTs) have demonstrated its efficacy against vertebral, nonvertebral, and hip fractures [2,3]. However, adherence is important to obtain the anti-fracture efficacy of bisphosphonates [4]. Monthly bisphosphonates, which are superior to weekly bisphosphonates in terms of patient preference, convenience, and treatment adherence (particularly persistence) [5,6], are widely prescribed. Recently, monthly risedronate has become available, and the usefulness of risedronate with a monthly dosing regimen is anticipated. The present review discusses the key characteristics of risedronate, three major Adverse Effects (AEs) of monthly bisphosphonates, specifically Osteonecrosis of the Jaw (ONJ), Atypical Femoral Fractures (AFFs), and Acute-phase Reactions (APRs), and the clinical outcome of monthly risedronate in patients with postmenopausal osteoporosis.

Key Characteristics of Risedronate

Chemically, bisphosphonates contain a phosphate-carbon-phosphate (P-C-P) bond that is resistant to biological degradation [7]. Various substitutions at positions R_1 and R_2 on the carbon atom define the specific pharmacologic properties and mechanisms of action of the different bisphosphonates.

The unique chemical structure of the bisphosphonates acts as a bone hook, allowing rapid and widespread distribution of bisphosphonates onto bone mineral surfaces [1]. Bisphosphonatebinding affinities for bone have potential clinical implications that are important in understanding differences among potent bisphosphonates. Bisphosphonates that share a common structure, with OH at R_1, can have different kinetic binding affinities for Hydroxyapatite (HAP), which must be attributed to differences in the R_2 side chain [8]. The nature of the R_2 side chain influences other surface properties, including zeta potential and interfacial tension. The affinity constants of major nitrogen-containing bisphosphonates for HAP growth differ according to a ranking of zoledronic acid > alendronate > ibandronate > risedronate [9]. Differences in binding affinities and effects on mineral surface properties are likely to be reflected in the clinical differences among bisphosphonates, including differences in potency, pharmacokinetics, and persistence of effect. These clinical differences may result from differences in uptake and retention on the skeleton, diffusion of the drug within bone, release of adsorbed drug from bone, potential recycling of the desorbed drug back onto bone surface, effects on mineral dynamic and effects on cellular functions [8]. Risedronate is substantially different from alendronate, ibandronate, and zoledronic acid in terms of quick attachment to bone and a short duration of effect because of its low affinity for bone.

Farnesyl pyrophosphate (FPP) synthase inhibition by bisphosphonates determines the antiresorptive potency. The specific structure of the R_2 side chain determines the biological activity and antiresorptive potency if the bisphosphonate molecule. Bisphosphonates containing nitrogen moieties at the R_2 site, including risedronate, ibandronate, alendronate, and zoledronic acid, are

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more potent as antiresorptive agents compared with non-nitrogen-containing bisphosphonates such as etidronbate [10]. The major nitrogen-containing bisphosphonates differ in synthase inhibition according to a ranking of zoledronic acid > risedronate > ibandronate > alendronate [11]. Nitrogen-containing bisphosphonates bind to and inhibit the activity of FPP synthase, a key regulatory enzyme in the mevalonic acid pathway that is critical to the production of cholesterol, other sterols, and isoprenoid lipids [9]. As such, the posttranslational modification (isoprenylation) of proteins, which play central roles in the regulation of core osteoclast cellular activities, is inhibited, ultimately leading to osteoclast apoptosis [9]. Thus, risedronate can effectively suppress bone turnover when used at a lower dosage, compared with alendronate and ibandronate, and this can be an advantage of risedronate for minimizing AEs.

The clinical consequences of the above differences among bisphosphonates could include skeletal retention of the drug, the speed of onset of effect, the speed of reversal of effect, the degree of bone turnover suppression, differences in bisphosphonate uptake in trabecular and cortical bone (effects on osteocyte function and survival), the types of anti-fracture effects, safety and tolerability. Risedronate reduces the risk of clinical vertebral and nonvertebral fractures in patients with postmenopausal osteoporosis within 6 months of the commencement of treatment [12,13]. Moreover, one year of discontinuation of risedronate treatment in patients with postmenopausal osteoporosis who had received 2 or 7 years of risedronate therapy led to increases in urinary NTX levels toward the baseline values and decreases in femoral trochanter and total hip BMD [14]. Thus, risedronate has the desirable pharmacological characteristics of rapidly reducing bone turnoverand reversing the effect. Furthermore, a comparison of the localization of compounds with differing mineral affinities in vivo, using fluorescent conjugates of risedronate and its low-affinity analogues deoxy-risedronate and 3-PEHPC, revealed that low-affinity compounds had a relatively higher degree of labeling of osteocyte lacunar walls and labeled lacunae deeper within cortical bone, indicating increased penetration of the osteocyte canalicular network [15]. Thus, risedronate is considered to enter the osteocyte canalicular network more readily than other bisphosphonates because of its low affinity for bone. Evidence also suggests the effectiveness of risedronate on osteocyte apoptosis caused by glucocorticoids in cortical bone [16].

Major AEs of Monthly Bisphosphonates

ONJ and AFFs are the major concerns in patients treated with bisphosphonates for long periods of time [17]. APRs are a concern in patients who begin monthly treatment with bisphospohonates [17].

According to the American Society for Bone and Mineral Research (ASBMR) Task Force Report, the risk of ONJ associated with oral bisphosphonate therapy for osteoporosis seems to be low and is estimated at between 1 in 10,000 and <1 in 100,000 patient-treatment years [18]. Risk factors in patients treated with oral bisphosphonates are i) dental extraction, oral bone manipulating surgery, poor fitting, dental appliances, and intraoral trauma; ii) duration of exposure to bisphosphonate treatment; iii) glucocorticoids; iv) co-morbid conditions; v) alcohol and/or tobacco abuse; and vi) pre-existing dental or periodontal disease [18]. Regarding AFFs, although the relative risks of AFFs are very high in patients receiving bisphosphonates, ranging from 2.1 to 128, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 person-years [19]. However, long-term use may be associated with a higher risk (>100 per 100,000 person-years) [19]. The risk factors are i) the long-term use of bisphosphonates (usually for more than 3 years; median treatment of 7 years), ii) glucocorticoid use or duration, iii) background rate of AFFs in osteoporosis patients, and iv) lower limb geometry and Asian ethnicity [19]. The risk for AFFs may decline after bisphosphonates are stopped [19]. Thus, these fractures are rare, particularly when considered against the incidence of common osteoporotic fractures of all types and of ordinary femoral neck and intertrochanteric fractures, all of which have been proven to decrease with bisphosphonate therapy.Thus, the incidences of ONJ and AFFs are so low that the following consensus has been reached: the benefit of bisphosphonates overwhelms the risk of bisphosphonates in terms of ONJ and AFFs [20].

The term “influenza-like illness” covers symptoms such as fatigue, fever, chills, myalgia, and arthralgia and is often referred to as an APR [21]. Symptoms of influenza-like illness are associated with monthly oral bisphosphonates [21]. These symptoms are transitory and self-limiting, usually lasting 1-3 days [21]. Normally, symptoms do not recur after subsequent drug administration [21]. The mechanism of APRs associated with nitrogen-containing bisphosphonates seems to be related to the inhibition of the mevalonate pathway, whereby the bisphosphonate induces the rapid and copious production of the proinflammatory cytokines tumor necrosis factor-α and interleukin-6 by γδT cells [22].

The risk factors and strategies for minimizing APRs have been investigated by large RCTs of intravenous zoledronic acid (5 mg once a year) in patients with postmenopausal osteoporosis. Reid et al. [23] reported that APRs were more common in non-Japanese Asians, younger subjects, and nonsteroidal anti-inflammatory drug users and was less common in smokers, patients with diabetes, previous users of oral bisphosphonates, and Latin Americans. All APR components had their peak onset within 1 day, the median duration of the APR was 3 days, and severity was rated as mild or moderate in 90% of the cases [23]. However, APRs rarely resulted in treatment discontinuation [23].

Bertoldo et al. [24] showed that women with APRs had significantly lower 25(OH)D levels than women without APRs and that the levels of 25(OH)D were normal (>30 ng/mL) in 31% of women with APRs and in 76% of women without APRs. The association between the APR and 25(OH)D suggests an interesting interplay among bisphosphonates, vitamin D, and the immune system [24].

Catalano et al. [25] reported that cholecalciferol at a dose of 300,000 IU reduced the intensity of musculoskeletal pain after the infusion of zoledronic acid. Silverman et al. [26] showed that acetaminophen taken 4 times/day for 3 days reduced the incidence and severity of post-dose symptoms following zoledronic acid infusion. Furthermore, Wark et al. [27] showed that acetaminophen/paracetamol or ibuprofen effectively managed the transient influenza-like symptoms associated with zoledronic acid.Consequently, the strategies for minimizing APRs after monthly risedronate therapy are considered i) to improve vitamin D insufficiency or deficiency prior to monthly risedronate therapy, ii) to start treatment using weekly risedronate and then to switch to monthly risedronate thereafter, and iii) to use acetaminophen or ibuprofen for 3 days just after the administration of monthly risedronate.

Monthly Risedronate

A Phase II RCT (dose-ranging study) was conducted to compare the tolerability and efficacy of 3 once-monthly risedronate dosing

regimens with those of risedronate administered at a dosage of 5 mg/day [28]. In total, 370 postmenopausal women aged 50-85 years with a lumbar spine T-score <-2.0 were randomly assigned to 1 of 4 treatment groups: risedronate at a dosage of 100, 150, or 200 mg/month or 5 mg/day (active control), administered orally for 6 months. The incidences of treatment-emergent AEs, serious AEs, and upper gastrointestinal AEs were not significant among the 4 groups. The mean percentage increases in BMD were 2.10%, 2.99%, and 3.38% with risedronate administered at a dosage of 100, 150, or 200 mg/month, respectively, vs. 3.05% at a dosage of 5 mg/day. At the 2 higher monthly doses, the changes in BMD from the baseline value were not significantly different from those obtained in the 5 mg/day group. The changes in bone turnover markers from baseline at 6 months at the 2 higher monthly doses were not significantly different from those obtained at 5 mg/day. Thus, the optimal dose of monthly risedronate was set at 150 mg.

A Phase III RCT was conducted to assess the efficacy and safety of a single monthly oral dose of 150 mg of risedronate compared with the 5 mg daily regimen [29]. In total, 1292 women with postmenopausal osteoporosis were randomly assigned to receive risedronate at a dosage of 5 mg/day or 150 mg/month in a double-blinded fashion. The primary efficacy endpoint was the mean percent change in lumbar spine BMD from the baseline value after 1 year. The mean percent change in the lumbar spine BMD was 3.4% in the daily group and 3.5% in the monthly group. The monthly regimen was determined to be non-inferior to the daily regimen based on prospectively defined criteria. The mean percent changes in BMD at sites in the hip (total proximal femur, femoral neck, and femoral trochanter) were also similar in both dosage groups, as were the changes in biochemical markers of bone turnover. The incidence of AEs, AEs leading to withdrawal, and upper gastrointestinalAEs were similar in both treatment groups. Both regimens were well tolerated. Thus, risedronate at 150 mg/month is similar in efficacy and safety to daily dosing and may provide an alternative for patients who prefer a monthly oral dosing regimen. However, the incidence of symptoms potentially associated with APRs (influenza-like illness and pyrexia starting within 3 days following the first dose of study drug and having a duration of 7 days or less), although low in both groups, was higher in the monthly group (1.4%) than in the daily group (0.2%)

Conclusions

Risedronate has the desirable pharmacological characteristics of rapidly reducing bone turnoverand reversing the effect. Risedronate is a first-line medicine for the treatment of postmenopausal osteoporosis. Monthly risedronate, which has been recently approved, is non-inferior to daily risedronate with regard to changes in surrogate markers and the incidence of AEs. However, the occurrence of APRs should be taken into consideration when monthly risedronate is prescribed. Because monthly bisphosphonates are superior to weekly bisphosphonates with regard to patient preference and convenience and, consequently, treatment adherence (particularly persistence), monthly risedronate is considered to be a useful treatment in clinical practice.

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