Risedronate's efficacy: from randomized clinical trials to real clinical practice

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Summary

Osteoporosis represents the most common human bone disorder with a large medical and economical burden on the Health Care System. Bisphosphonates are the major drugs used for the treatment of osteoporosis. Differences in their chemical structures and pharmacokinetic actions can explain the different clinical efficacy among these molecules. Risedronate is a potent inhibitor of farnesyl pyrophosphate synthase, but does not bind strongly to mineral; this lower mineral binding may enable risedronate to have a wider distribution in bone. Its antifracture efficacy has been established in several randomized phase III controlled studies that showed its value in the reduction of vertebral, non vertebral and hip fractures. Randomized controlled trials and observational studies demonstrated risedronate efficacy and safety in different subsets of patients, therefore risedronate is configured, among oral therapies currently available for osteoporosis, as a drug of first choice.

KEY WORDS: risedronate, osteoporosis, drug therapy.

Introduction

Osteoporosis is the most common human bone disorder. It is characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to enhanced bone fragility and a consequent increase in fracture risk (1).
It places a large medical and economic burden on the Health Care System and it is expected to become even more common and costly because of increasing longevity (2). By the year 2050, the incidence in the world of hip fractures, the most serious outcome of osteoporosis, is expected to increase by 240% in women, and 310% in men (3).
Bisphosphonates, the most used drugs in the treatment of osteoporosis, are a very good therapy to reduce the risk of fracture, and morbidity and mortality associated. They bind to hydroxyapatite (HAP) in bone and effectively suppress bone resorption by interfering with osteoclastic activity.
There are important differences among chemical structure of bisphosphonates which may explain the different bind to bone mineral and some differences in efficacy, speed of onset and offset action and safety (4).

Chemical features of risedronate

Bisphosphonates contain a chemical backbone of carbon and phosphorus in the arrangement -P-C-P-.
Non-nitrogen-containing bisphosphonates (N-BPs) act by incorporation into ATP, whereas alkyl aminobisphosphonates act by farnesyl pyrophosphate synthase (FPPs) inhibition. The heterocyclic N-BPs, as Risedronate, also inhibit the FPPs enzyme and stabilize its conformation change that magnify their inhibitory potency (4). Risedronate is a unique pyridinil bisphosphonate.
The R1 and R2 side-chains attached to the carbon atom are responsible for the range of activity observed among bisphosphonates.
Bisphosphonates have in particular two features that influence their action on bone:

- osteotropism with a strong affinity for hydroxyapatite: the affinity for the bone and its mineral component affects two key moments in the pharmacology of the molecules: their uptake and release (the avidity for bone, the distribution on it and the cessation of pharmacology);
- the metabolic action on the skeletal system: the binding affinity of farnesyl pyrophosphate synthase and its inhibition modulate the function of osteoclasts and therefore their resorptive potency; recent studies have shown also an action favoring the function of osteocytes and osteoblasts.

Overall, the different activities of the various bisphosphonates on the market can be attributed to differences in their affinity towards the mineral component of bone, and the different inhibitory potency against the enzyme FPPs.
The order of potency in inhibiting FPPsynthase is zoledronate > risedronate > ibandronate > alendronate.
The order in the kinetic binding affinity to HAP is clodronate < etidronate < risedronate < ibandronate < alendronate < pamidronate < zoledronate (3).
Risedronate is, therefore, a potent inhibitor of FPPs, but does not bind strongly to mineral; this lower mineral binding may enable risedronate to have a wider distribution in bone (3).
These data may explain the pharmacological efficacy of risedronate, such as speed of action, and influence some aspects of molecular pharmacology, such as the half-life in bone tissue that for risedronate is on the order of weeks. The accumulation in bone could lead to a marked inhibition of the turnover during long-term therapy and a persistence of inhibition after cessation of therapy. Risedronate reduces bone turnover by 50%, but after 12 months of stopping treatment, the bone turnover, assessed with the same parameters, returns to baseline (5).
These aspects could influence choices in prolonged and cyclical treatments and therapies and may also affect the effectiveness of other concomitant therapy for osteoporosis other than bisphosphonates.
In the recent study OPTAMISE (Clinical Effectiveness of Teriparatide After Alendronate or Risedronate therapy in postmenopausal osteoporotic women) were evaluated women with

post-menopausal osteoporosis previously treated with risedronate or alendronate on the subsequent response to the administration of teriparatide.
Patients treated with risedronic acid before treatment with teriparatide had a greater anabolic response than those previously treated with alendronic acid (6).

Efficacy of Risedronate

Treatment of postmenopausal osteoporotic subjects with risedronate reduces fractures while concomitantly preserving bone microarchitecture and increasing bone mineral density.
Risedronate has been available since 2000 and its antifracture efficacy has been established in several randomized phase III controlled studies.

Vertebral and non vertebral data

Risedronate demonstrated to reduce vertebral and non vertebral fractures in postmenopausal women with a history of vertebral fracture in two clinical studies, VERT- North America (VERT-NA) (7) and VERT-Multinational (VERT-MN) (8).
A significant reduction was observed in the risk of new vertebral fractures by 65% ($p < 0.001$) and 61% ($p = 0.001$) after the first year of treatment with risedronate in VERT-NA and VERT-MN studies, respectively. This effect was maintained throughout the treatment period (3 years), with significant reduction in the incidence of new vertebral fractures by 41% ($p = 0.003$) in VERT-NA and by 49% in VERT-MN ($p < 0.001$).
In VERT-NA the significant anti-fracture efficacy was demonstrated the first year in a population at high risk (i.e. patients with at least 2 or more vertebral fractures): the risk reduction was 74%.
Risedronate has also been shown to significantly reduce the risk of nonvertebral fractures by 39% ($p = 0.02$) after 3 years in VERT-NA.
In postmenopausal women with low bone mineral density (BMD) with or without prevalent vertebral fractures enrolled in four phase III studies, risedronate reduced the risk of vertebral osteoporotic fractures by 74% ($p = 0.001$) (9).

Hip data

Hip fractures are the most serious outcome of osteoporosis because of the associated morbidity, mortality, and costs. The Hip Intervention Program on 9.331 patients was the first and largest clinical study on a bisphosphonate having as primary objective to assess its efficacy on femoral fractures (10). The results demonstrated that treatment with risedronate significantly reduces the risk of hip fractures in osteoporotic women.
In the general population, risedronate reduced the risk of fractures by 30% ($p = 0.02$).
The risk reduction was 41% versus placebo over 3 years in women with low bone mineral density at the femoral neck and 60% versus placebo in women with low bone mineral density at the femoral neck and at least one prevalent vertebral fracture.

Fast action

The speed of action is a feature of great importance for two reasons:
- the previous fragility fracture is the most important risk factor of new fractures and the risk is highest within the first year after fracture (11)
- the mean time of adherence to therapy is about 8 months (12), so the faster a drug is, the more the patient will actually benefit from its therapeutic efficacy.

Risedronate is the only bisphosphonate that has been shown to reduce significantly the risk of both vertebral and non vertebral fractures in 6 months of therapy (13, 14).
The increased speed of action was also demonstrated in patients with corticosteroids induced osteoporosis, in which risedronate reduced by 70% ($p < 0.01$) the risk of vertebral fractures at one year in both genders (15).

Long term efficacy

Osteoporosis is a chronic disease, therefore needs a medium-long term therapy.
In order to determine the effects of 5 years of risedronate treatment, Sorensen et al. performed an extension of a 3-year, placebo-controlled study in 265 post-menopausal women, with at least two prevalent vertebral fractures for an additional 2 years: after this period risedronate demonstrated its efficacy in reducing the risk of new vertebral fractures by 59% (incidence of vertebral fractures in the risedronate group 13.8%, incidence in the placebo group 28.2%: $p = 0.01$) (16).
Similar levels of risk reduction were maintained in a further extension of two years of the original study (total duration of 7 years) (17).

Observational studies

Randomized controlled trials (RCTs) are the gold standard for determining drug efficacy and safety. RCTs are designed to minimize internal bias and to maximize treatment effect. However, their design creates shortfalls with regards to external validity of the outcomes.
Many patients with osteoporosis, in fact, can not be included in standard RCTs because of co-morbidities and prior therapies.
REAL retrospective study carried out on 34000 patients showed rapid effectiveness of risedronate (18). After a year of therapy with risedronate 35 mg/week the incidence of hip fractures (-43%, $p = 0.01$) and nonvertebral fractures (- 18%: $p = 0.03$) is lower than in patients treated with alendronate 70 mg / week.
In a recent real life study (CLEAR study, Longitudinal Change in Clinical Fracture Incidence After Initiation of Bisphosphonates) (19), administrative database were used to follow three cohorts of women aged 65 and older (total n = 210,144) after starting therapy either on alendronate, risedronate, or ibandronate in the USA between market introduction and 2006. Within each cohort, the baseline incidence of clinical fractures at the hip, vertebral, and nonvertebral sites was defined by the initial 3-month period after starting therapy. Relative to these baselines, the authors then compared the fracture incidence during the subsequent 12 months on therapy. Relative to the baseline incidence, fracture incidence was significantly lower in the subsequent 12 months in both cohorts of alendronate (18% lower at hip, 28% at nonvertebral sites, and 57% at vertebral sites) and risedronate (27% lower at hip, 21% at nonvertebral sites, and 54% at vertebral sites). In the ibandronate cohort, the fracture incidence was lower (31%) only at vertebral sites. The reductions observed in fracture incidence over time within each cohort suggest that the effectiveness of each bisphosphonate in clinical practice has been consistent with their efficacies demonstrated in randomized controlled trials.

Risedronate efficacy in different subsets of patients

Risedronate is also indicated for osteoporosis in men. In 316 men with primary or secondary osteoporosis, risedronate 5 mg/day significantly reduced by 60% the incidence of new vertebral fractures after one year of therapy (incidence of vertebral fractures in the risedronate group 5.1%, incidence in the placebo group 12.6% $p = 0.028$) (24) and significantly reduced by 61% the incidence of new vertebral fractures after two years of therapy (incidence of vertebral fractures in the risedronate group 9.2%, incidence in the placebo group 23.6%, $p = 0.0026$) (25). Risedronate significant-

ly reduced by 45% the incidence of new nonvertebral fractures after two years of therapy (incidence of nonvertebral fractures in the group risedronate 11.8%, incidence in the placebo group 22.3%, $p = 0.032$) (25).
In a study on 284 men with primary osteoporosis it was shown an increase of BMD at the lumbar spine, statistically significant (4.5%, $p < 0.0001$) in patients treated with risedronate 35 mg once a week compared to placebo. This effect was already significant after the first 6 months of treatment (2.6%, $p < 0.0001$) (26).
In another study, risedronate demonstrated to increase BMD and to reduce hip fractures in elderly poststroke men (27).
There is a high incidence of hip fractures in patients after hemiplegic stroke, and bone mineral density is decreased on the hemiplegic side in these patients, correlating with the immobilization-induced bone resorption, the degree of paralysis, and hypovitaminosis D; the purpose of this study was to evaluate the effectiveness of risedronate on osteoporosis and the risk of hip fractures in men 65 years or older after stroke. Risedronate significantly reduced by 81% the incidence of hip fracture (95% confidence interval, 0.04-0.89).
Risedronate has been shown to reduce proximal bone resorption around the femoral stem in patients with total hip arthroplasty (evaluation of bone mineral density in the seven Gruen zones and markers of bone turnover) (28, 29).

Tolerability

In general, there is a good safety profile for bisphosphonates.
To review the frequency of upper gastrointestinal (GI) events with risedronate, Taggart et al. pooled nine multicenter, randomized placebo controlled studies on risedronate (30).
Sixty percent of patients had a history of GI tract disease, 38.7% had active GI tract disease, and 20.5% used antisecretory drugs during the studies. Sixty-three percent used aspirin and/or nonsteroidal anti-inflammatory drugs during the studies. Upper GI adverse events were reported by 29.6% of patients in the placebo arm compared with 29.8% in the risedronate arm. In addition, endoscopy performed in 349 patients demonstrated no significant difference among the two groups.
Renal side effects were also studied, given that bisphosphonates are cleared by the kidney. Miller et al. pooled the results of nine clinical trials, revealing no significant differences in incidence of renal toxicity between daily risedronate and placebo with baseline renal function being the same between the two groups. Risedronate was found to have no effect on specific renal function or general adverse events across mild, moderate, and severe age-related renal dysfunction (31).

Conclusions

Based on the RCTs and observational studies, for the proven efficacy on all skeletal sites and the high safety profile, risedronate is configured, among oral therapies currently available for osteoporosis, as a therapy of first choice.

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