

# New dosing options in osteoporosis treatment: clinical evidence on Risedronate 75mg monthly treatment

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## Summary

Prevention of osteoporosis fractures is currently possible by implementing lifestyle changes as well as with effective treatments. The role played by different agents is particularly important in reducing the risk of hip fracture, which is certainly the most severe consequence of osteoporosis in terms of deteriorating quality of life for the patient, reduced life expectancy and health care costs.

In order to choose an adequate treatment, therapies with well-established efficacy should be considered. In addition, for medical treatment success, patient adherence is essential. Recently published clinical data show that risedronate 75mg, administered monthly on two consecutive days, equivalent to risedronate 5 mg daily in terms of BMD changes, bone turnover markers and incidence of new vertebral fractures, and has an equivalent safety profile. The new risedronate 75mg monthly formulation, administered on two consecutive days, is therefore the first and only oral monthly therapy with proven efficacy in reducing the risk of vertebral, non-vertebral and hip fractures, and a safety profile confirmed by Phase III trials and 8-year post-marketing experience of risedronate. Monthly dosing may offer the advantage of improving patient compliance and persistence on the treatment, thanks to the less frequent administration.

*KEY WORDS: Risedronate, monthly therapy, adherence to therapy.*

## Introduction

Osteoporosis is a chronic skeletal disease, characterized by reduced BMD and bone micro-architecture alterations and increased fracture risk (1). This pathological condition has a considerable clinical and epidemiological impact on the population all over the world. The most important clinical consequence of osteoporosis is the hip fracture, an event that is strongly associated with patient mortality and disability, and has economic implications in terms of increased health care costs (2). The choice of an adequate osteoporosis treatment should be based on a number of fundamental characteristics, including efficacy

in reducing risk of fractures, speed of action, effects in different skeletal sites, long term efficacy safety and tolerability. Currently, bisphosphonates are the treatment of choice to control osteoporosis and prevent severe complications due to vertebral, non-vertebral and hip fractures (3). Similarly to other chronic conditions, improved treatment adherence is a priority goal. In fact, frequency of administration has been demonstrated to affect patient compliance and persistence on treatment, and therefore treatment efficacy. Nowadays the persistence on treatment with bisphosphonate is unacceptably low (4, 5). Persistence increases by extending Bisphosphonate dosing intervals (6), even though dosage is not the only factor determining treatment compliance. Knowledge of drug efficacy and safety profile has been demonstrated to be more important than dosing frequency in patient preference and compliance to Bisphosphonate treatment (7, 8). Recent studies have been conducted to demonstrate the efficacy of new therapeutic approaches based on monthly dosing of bisphosphonates (9).

## As demonstrated by Evidence Based Medicine, Risedronate provides risk fracture protection in all skeletal sites

In the framework of bisphosphonate treatment, there are evidences on risedronate efficacy and use of this agent is included in important national and international guidelines on osteoporosis treatment. As demonstrated by randomized clinical trials (10-12), the efficacy of Risedronate is confirmed in terms of vertebral and non-vertebral fracture risk reduction and in terms of safety.

Risedronate efficacy in hip fracture risk reduction has been demonstrated in the HIP trial (Hip Intervention Program), conducted on 9,331 patients at hip fracture risk. In the group of patients with low BMD and at least one prevalent vertebral fracture, risedronate has been proven to reduce hip fracture incidence by 60% ( $p=0.003$ ) compared with the placebo group treated with Calcium and Vitamin D (13).

It is worth mentioning that efficacy of Ibandronate on hip fracture has not been established. Moreover, regarding the efficacy on non-vertebral fractures, the BONE trial (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe), conducted on about 2,000 patients, showed no statistically significant difference vs. placebo in terms of incidence of non vertebral fracture events at 3 years after treatment with oral Ibandronate either daily (2.5mg) or intermittently (20mg every other day for 12 doses every three months) (14).

Clinical trials demonstrate risedronate speed of action in reducing the risk of vertebral (15) and nonvertebral (16) clinical fractures at 6 months.

In terms of risedronate antifracture effectiveness, the results of randomized clinical trials are confirmed by the results of REAL (Risedronate and ALendronate) Observational Study conducted on health care databases. The REAL trial showed that treatment of osteoporosis patients ( $n = 33,830$ ) with risedronate vs alendronate at a weekly dosage significantly reduced the incidence of hip fracture events at 6 months (-46%,  $P = 0.02$ ) and at 12 months (-43%,  $P = 0.01$ ) (17).

In terms of safety and tolerability data, 7-year follow-up data of

patients enrolled in Phase III trials show good tolerability profile of risedronate and maintenance of antifracture efficacy profile (18).

**New data on Risedronate 75mg monthly treatment show equivalent efficacy as Risedronate 5 mg daily dosing**

Recently has been approved, in Italy and in other European countries, the new formulation of Risedronate 75mg on two consecutive days each month for osteoporosis treatment. The following data illustrate the Phase III results of a recent study by Delmas and co-workers (19). The study design included 24-month treatment of postmenopausal women with osteoporosis with risedronate 75 mg.e. or 5 mg daily. It was randomized, double-blind trial including over 1,200 patients recruited in different international centres, aged  $\geq 50$  years with lumbar BMD  $<-2.5$  or  $<-2.0$  with one prevalent vertebral fracture. The patients were blindly randomized to risedronate 5mg daily or 75mg two consecutive days each month and placebo for the rest of the month. Supplementation with Calcium (1000mg daily) and Vitamin D (400-800 IU daily) was prescribed. The trial was designed to assess the percent change from baseline in lumbar (LS), total hip, trochanter and femoral neck BMD at 6 and 12 months. The incidence of morphometric vertebral fractures was assessed by X-ray measurements from baseline to months 12. Biochemical markers of bone turnover (sBAP, serum bone-specific alkaline phosphatase; uNTX, urinary type-1 collagen N-telopeptide) were measured at 3, 6 and 12 months. Safety was assessed based

on adverse event incidence, clinical examination and routine laboratory tests.

Data at 12 months show no significant difference in terms of LS BMD changes (Fig. 1). Bone turnover markers decreased with both treatments at 3, 6 and 12 months (Fig. 2). Incidence of new vertebral fractures at 12 months was the same in the two groups (Fig. 3). Identification of clinical vertebral and non-vertebral fractures as adverse events was similar in the two groups. Safety data were favourable, with good general tolerability. There were no clinically significant differences in physical examinations or laboratory measures between treatments. Adverse events were generally similar between treatments, including GI Aes (Fig. 4).

The results of the study by Delmas et al. show equivalence of Risedronate 75 mg on two consecutive days each month to the 5 mg daily regimen both in terms of efficacy and safety, providing the first oral monthly treatment available so far for osteoporosis, with a complete efficacy profile on vertebral, non-vertebral and hip fractures, with the opportunity to improve patient adherence with a less frequent dosing regimen.

As an additional confirmation of the antifracture efficacy of the less frequent dosing regimen the groups in the risedronate 75 mg Phase III trial were compared with a historical cohort of patients in the placebo arms of VERT trials (Vertebral Efficacy of Risedronate Therapy). In presenting the results at the 2007 Congress of the American Society for Bone and Mineral Research (ASBMR), Watt and co-workers explained their alternative choice of "historical" controls by underlying that the recruitment of placebo groups in new trials to confirm favourable results is limited by practical, and especially by bioethical consid-

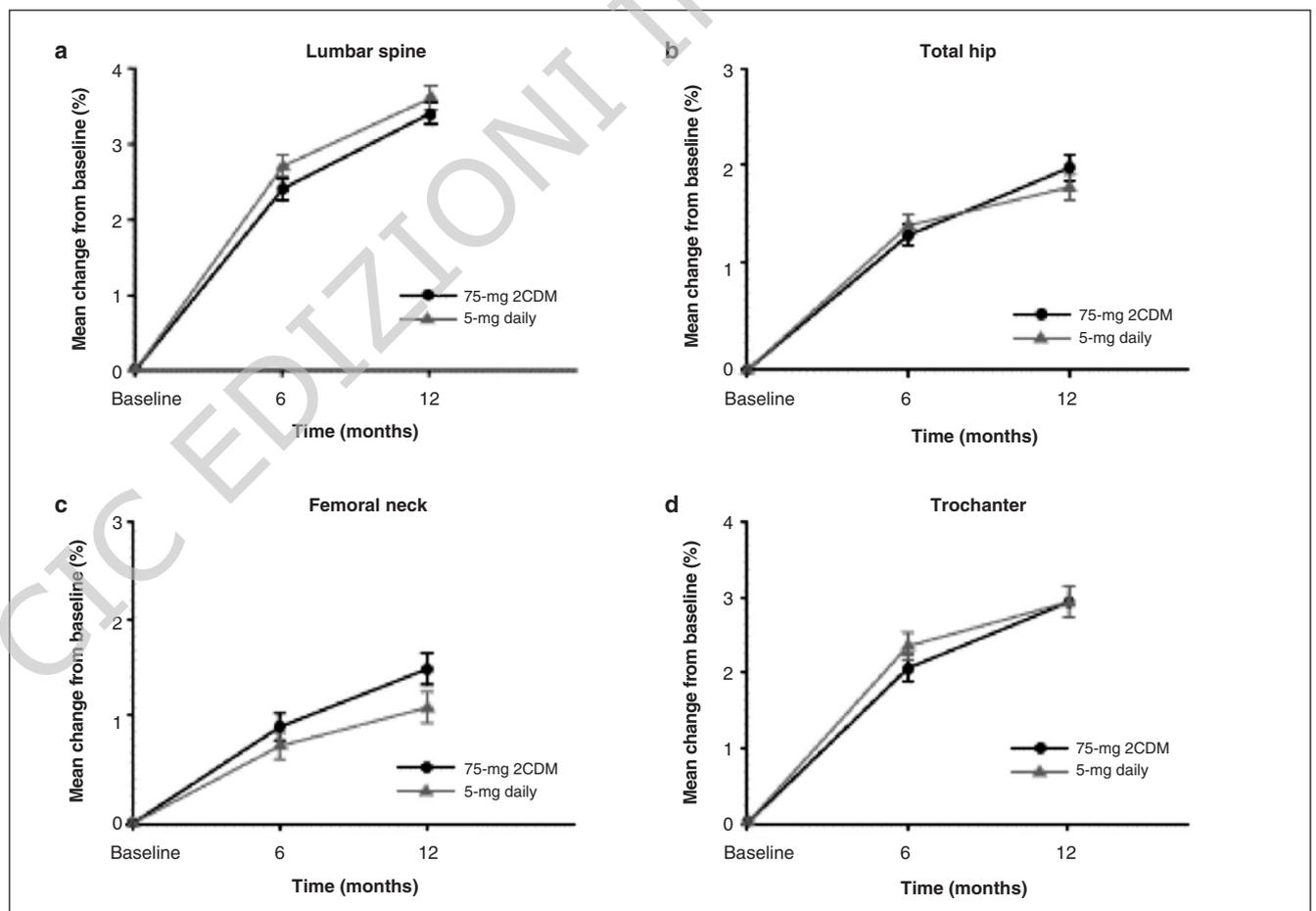


Figure 1 - Mean percent change in BMD of the lumbar spine, total hip, femoral neck and trochanter.

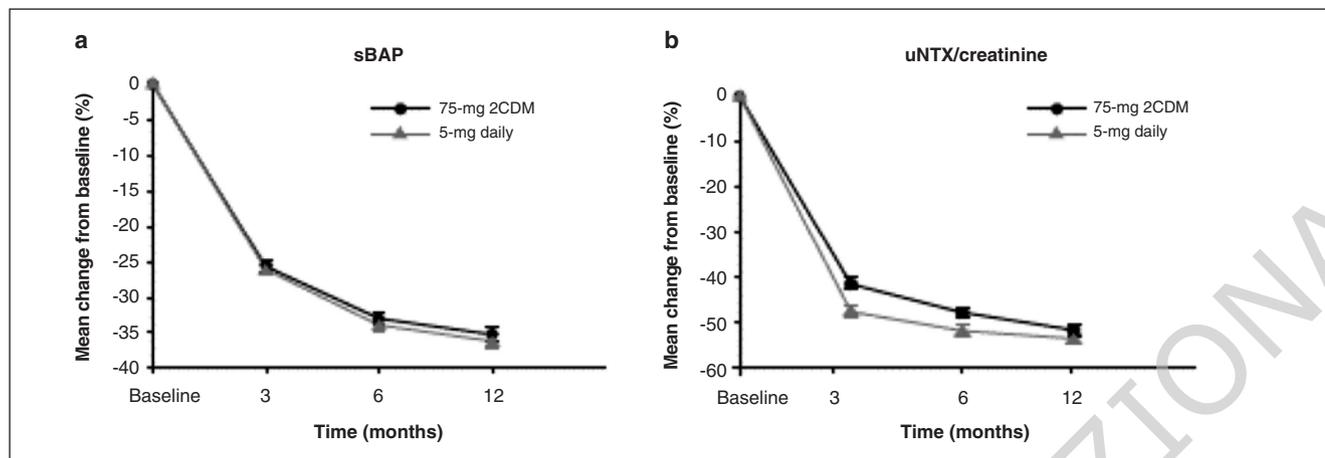


Figure 2 - Mean percent change from baseline in bone turnover markers.

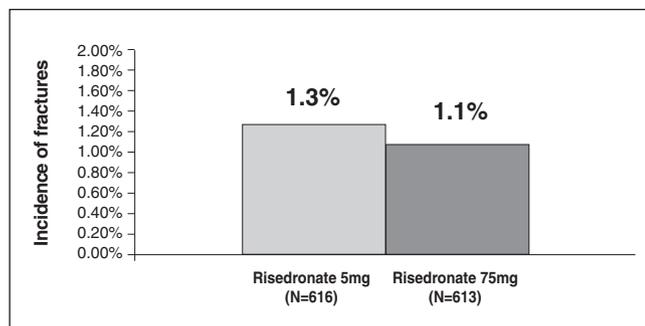


Figure 3 - Incidence of new vertebral fractures at 12 months.

erations (20). In the “historical” placebo group, 99 patients from the VERT trials were included with homogeneous clinical and demographic characteristics (age, years since menopause, BMD and incidence of previous vertebral fractures) with respect to the patients enrolled in the risedronate 75mg trial. The same criteria were used in the recruitment of a fourth group of 96 patients treated with risedronate 5mg daily in the VERT tri-

als (5mg “historical” group). Retrospective comparison of data after 12 months of treatment confirmed that the risk of new vertebral fractures in the risedronate 75mg group was less than 79% vs the “historical” placebo group ( $p = 0.016$ ), the reduction being similar to the VERT MN and NA trials (61 and 65%, respectively) on active treatment with risedronate 5 mg daily (Fig. 5). Moreover, the incidence of new vertebral fractures (internal validation test) was similar in the 3 groups in active treatment. Therefore, monthly risedronate dosing leads to considerable BMD improvement in patients with postmenopausal osteoporosis, similarly to risedronate 5mg, with a similar antifracture efficacy as the conventional daily treatment and a 79% reduction in the risk of new vertebral fractures in the first year of treatment vs the historical placebo group.

**Risedronate 75mg is the monthly treatment with the broadest antifracture efficacy**

The increasing amount of evidence available has enabled the US (FDA) and European Regulatory Authorities to approve the monthly risedronate 75 mg on two consecutive days each month, with proven antifracture efficacy and safety similar to

Risedronate 75 mg Phase III Study Selected Adverse Event Incidence at Month 12		
Adverse events	RIS 5 mg (N = 613)	RIS 75 mg (N = 616)
Serious TEAEs	4.7% (29)	7.5% (46)
Possibly or probably related serious TEAEs	0.5% (3)	0.6% (4)
Upper GI TEAEs	21.2% (130)	22.2% (137)
Moderate to sever Upper GI TEAEs	6.2% (38)	7.5% (46)
Arthralgia	9.5% (58)	10.4% (64)
Back pain	10.8% (66)	8.8% (54)

Figure 4

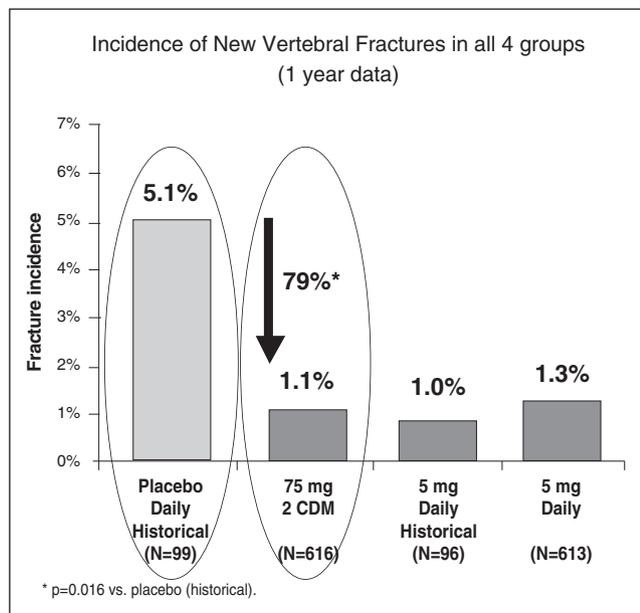


Figure 5 - Risedronate 75 mg Matched Historical Control Study to assess Anti-Fracture Efficacy.

daily 5 mg risedronate. Risedronate 75mg provides a new and effective option for postmenopausal osteoporosis treatment and prevention of fractures offering patients the option of a less frequent dosing regimen and the opportunity to improve adherence and consequently obtain optimal long-term control of osteoporosis. Moreover, risedronate efficacy data at 6 months of treatment (15, 16) provide a peculiar efficacy profile to meet the growing health care needs due to frequent and burdensome fragility fractures.

Both new clinical trials and observational studies have confirmed that risedronate provides a convenient therapeutic option for osteoporosis, being the only drug available for oral monthly administration in its category, with proven antifracture efficacy on vertebral and non-vertebral fractures.

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