# Evidence-based Rheumatology

*edited by M. Matucci Cerinic*

## Risedronate increases bone mineral density and reduces the vertebral fracture incidence in postmenopausal women

**Author:** S.T. Harris *et al.*
**Title:** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis
**Source:** *JAMA*, vol. 282, October 1999, pgs. 1344-52.

**Aim:** Risedronate (Ris) is a pyridinyl bisphosphonate with potent anti-resorptive activity, effective in the treatment of Paget's disease and multiple myeloma, and for the prevention of bone loss in early postmenopausal women. The aim of the study was to determine the efficacy of risedronate in reducing the incidence of vertebral and other fractures in postmenopausal women with previous vertebral fractures, and to assess its safety. The study was designed as a multicenter, randomized, double blind, placebo controlled parallel group trial.

**Methods:** 2,458 women out of the 9,400 screened at 110 study centers in North America met the following criteria: age < 85 years, natural or surgical menopause lasting at least 5 years, 2 or more identified vertebral fractures (T4-L4) or 1 vertebral fracture and low BMD, with a T score of -2 (2 standard deviations below the mean for young adults). Women were excluded if they had conditions that might interfere with the evaluation of spinal loss or if they had recently received drugs affecting bone metabolism (calcitonin, cholecalciferol, calcitriol, anabolic steroids, estrogen or estrogen-related drugs, progestins, bisphosphonates, fluoride).

Pts were stratified based on the baseline number of vertebral fractures (stratum 1: pts with 1 vertebral fracture and low baseline BMD; stratum 2: subjects with > 2 baseline vertebral fractures) and were randomly assigned to 1 of 3 treatment groups: risedronate 5 mg/d, risedronate 2.5 mg/d, or placebo. All participants received a calcium supplement (1000 mg of elemental calcium daily) and subjects with low serum 25-hydroxyvitamin D levels at baseline (< 40 nmol/L) also took cholecalciferol supplements (up to 500 IU/d).

The incidence of new vertebral fractures (T4-L4) was expressed as the proportion of subjects with at least 1 incident fracture over 3 years of study. New and worsening vertebral fractures (fractures in previously normal vertebrae and worsening fractures in already fractured vertebrae) were also examined. Lateral thoracic and lumbar spine radiographs were taken at baseline and annually throughout the study. Quantitative and semiquantitative assessments were used to identify both prevalent (baseline) and incident vertebral fractures for the purpose of efficacy determinations.

Vertebral (L1-L4), femoral and radius BMD was measured by dual-energy x-ray absortiometry at baseline and at 6-month intervals throughout the study. Radiographically confirmed non-vertebral fractures (at the clavicle, homerus, wrist, pelvis, hip or leg, whether or not associated with trauma) were recorded. Biochemical markers of bone turnover (bone-specific alkaline phosphatase and the deoxypyridinoline/creatinine ratio) were only determined in subjects in some study centers.

All participants received a physical examination at baseline and at the end of the study. Vital signs and standard hematology and clinical chemistry tests were performed at regular study visits and adverse events were recorded. Endoscopy was performed in some subjects who complained of gastrointestinal symptoms. In selected centers an iliac crest bone biopsy was obtained at baseline and post-treatment following double tetracycline labeling in order to determine the safety of Ris on bone.

The planned study duration was 3 years. Data from other studies published after the trial was begun indicated that the 2.5 mg dosage was less effective than 5 mg, and so the 2.5 mg Ris treatment arm was discontinued after the first year. Therefore, the prospectively defined primary analysis compared the 5 mg Ris and placebo groups at the 5% significance level. Efficacy analysis was performed on an intention-to-treat basis. At baseline, continuous variables were compared by analysis of variance (ANOVA). Discrete variations were compared by the Cochran-Mantel-Haenszel test. For the analysis of the vertebral and non-vertebral fracture incidences, the placebo and 5 mg Ris groups were compared by a stratified log-rank test. The relative risk of fractures between the 5 mg Ris and the placebo groups was calculated by a stratified Cox proportional hazard regression model. The fracture incidence was calculated using the Kaplan Meier method, and BMD and bone turnover markers were analyzed by ANOVA.

**Results:** 2,458 women out of 9,400 screened were randomized: 19 were not treated (9 due to protocol violations and 10 due to voluntary withdrawal), 815 received placebo, 811 received Ris 2.5 mg, and 813 received Ris 5 mg. Across the treatment groups a total of 1,847 subjects (75.7%) completed 1 year of treatment. The 2.5 Ris arm was discontinued by protocol amendment after the first year; 55% (450 pts) of the placebo group and 60% (489) of the 5 mg Ris group completed 3 years of treatment.

Compared with placebo, treatment with 5 mg/d of Ris decreased the cumulative incidence of new vertebral fractures by 41% (95% confidence interval [CI], 18% - 58%) over three years (11.3% vs 16.3%; P = 0.003). A fracture reduction of 65% (95% CI, 38% - 81%) was observed after the first year (2.4% vs 6.4%; P < 0.001). The cumulative incidence of non-vertebral fractures over 3 years was reduced by 39% (95% CI, 6% - 61%) (5.2% vs 8.4%, P = 0.02). BMD increased significantly compared with placebo at the lumbar spine (5.4% vs 1.1%), femoral neck (1.6% vs -1.2%), femoral trochanter (3.3% vs -0.7%), and the midshaft of the radius (0.2% vs -1.4%).

Bone turnover markers were available for 775 out of 2,458 pts. Specific alkaline phosphatase values at the end of 3

years of treatment were -33% in the 5 mg Ris group vs -7% in the placebo group, while deoxypyridinoline-creatinine ratio values were -26% vs -1% in the same groups.
The 31 pts (from both the placebo and 5 mg Ris groups) who underwent bone biopsy at baseline and at the end of treatment had histologically normal bone. The overall safety profile of Ris, including gastrointestinal safety, was similar to that of placebo. Digestive system complaints (mainly dyspepsia, abdominal pain and gastritis) were the most common adverse events associated with study discontinuance: 56 pts (42%) from the placebo group and 49 pts (36%) from the 5 mg Ris group withdrew for this reason.
**Conclusions:** These data suggest that in postmenopausal women affected by osteoporosis, 3 years of therapy with 5 mg risedronate increases BMD at vertebral and femoral sites, reduces bone turnover, reduces the risk of vertebral and non-vertebral fractures, and overall is as safe as placebo.

**Comment**

*This manuscript describes the effect of risedronate, a pyridinyl bisphosphonate, on bone mineral density and fracture (vertebral and non-vertebral) rates over 3 years. Risedronate was previously successfully used in the treatment of Paget's disease of bone and multiple myeloma and in the prevention of bone loss in early menopause. The study of Harris and colleagues forms part of a large programme aimed at evaluating the efficacy and safety of risedronate in postmenopausal osteoporosis. While the present study reports results in a population with at least one vertebral fracture at baseline, encouraging results have also been reported in women with low bone mineral density and no prevalent fracture (1), two or more prevalent vertebral fractures (2), and in elderly women with either low bone mineral density or non-skeletal risk factors for hip fracture (3).*
*The Harris study demonstrates that risedronate significantly increases bone mineral density compared with placebo at all meaningful skeletal sites and significantly reduces new vertebral fractures and non-vertebral fractures over 3 years. The major strength of this study is its up-to-date methodology; comparing risedronate with placebo in a double-blind prospective long-term study, the rapid onset of action of risedronate was demonstrated through a significant reduction of the fracture rate at the spine after one year and the effect on non-spinal fractures, in a study which was primarly designed and powered to demonstrate only an effect on the spine.*
*The safety profile of risedronate appears to be comparable to that of placebo. Since similar findings were reported in the Fracture Intervention Trial, which assessed the efficacy and safety of alendronate (an amino-bisphosphonate) in osteoporosis, it will be interesting to see whether gastrointestinal tolerance will be as good when risedronate is dispensed in the real world, outside of a clinical trial. However, it is a shame that the 2.5 mg dose of risedronate was discontinued after 12 months. The results obtained after one year suggest that the low dose was also inducing a significant increase in BMD and a significant reduction in spinal fracture rates. Since most of the gastrointestinal toxicity of bisphosphonates is dose-related, clinicians might be interested in using 2.5 mg daily instead of the recommended 5 mg dose.*
*The major drawback of the study is that most,if not all, of the antifracture efficacy of the 5 mg dose, in terms of the reduction of fractures, appears to have occurred during the 12 first months of the study. Comparison of the fracture rates in the 5 mg group and in the placebo group during the last two years of the trial do not show a significant effect for risedronate. This does not compare favourably with the results published for alendronate and raloxifene. In terms of the rational use of health resources,one should consider limiting the duration (or the reimbursement) of risedronate to a 12-month period.*
*In conclusion, Harris and colleagues have shown that risedronate given to women with low bone mineral density and prevalent fractures can significantly increase bone mineral density at relevant skeletal sites and decrease vertebral and non-vertebral fractures (with no specific effect shown at the hip). However, taking into account the uncertainties related to the most appropriate dosage and the long-term gastrointestinal safety of risedronate in the real life setting, and the absence of anti-fracture efficacy after the first year of treatment, this medication at the dose recommended (5 mg) should probably only be considered for patients intolerant or resistant to alendronate and raloxifene.*

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**References**

1. FOGELMAN I,RIBOT C,SMITH R,ETHGEN D, SOD E,REGINSTER JY for the BMD-MN Study Group: Risedronate reverses bone loss in postmenopausal women with low bone mass: Results from a multinational double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; 85:1895-1900.
2. REGINSTER JY, MINNE HW, SORENSEN OH *et al.* on behalf of the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group:Randomized trial of effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporosis Int* 2000; 11:83-91.
3. MCCLUNG M,GEUSENS P, MILLER P *et al.* for the Hip Intervention Program Study Group: Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001; 344: 333-40.

## Etanercept improves active polyarticular juvenile rheumatoid arthritis

**Authors:** D.J. Lovell *et al.*
**Title:** Etanercept in children with polyarticular juvenile rheumatoid arthritis
**Source:** *N Engl J Med* 2000; 342: 763-9

**Aim:** Juvenile rheumatoid arthritis (JRA), the most common rheumatic condition in children, requires aggressive therapy in almost two-thirds of patients. Methotrexate (MTX) is efficacious and well tolerated in JRA patients with polyarticular involvement requiring disease modifying antirheumatic

drugs (DMARDs), but sometimes induces only a partial remission of RA and causes side effects. For this reason, a randomized, multicenter, double blind trial was conducted to test whether etanercept, a soluble tumor necrosis factor receptor (p75): Fc fusion protein, may provide benefit to polyarticular juvenile rheumatoid arthritis (PJRA) patients (pts) who either do not tolerate or show an inadequate response to MTX.

**Methods:** Sixty-nine PJRA pts (43 females and 26 males), aged 4-17 years (MEDIUM age 10.5 years) were enrolled. MTX and other DMARDs were discontinued 14 and 28 days, respectively, before the beginning of the study. Stable doses of nonsteroidal antiinflammatory drugs and low doses of corticosteroids were allowed. The trial was divided into two parts. In the first part, an open-label study whose aim was to evaluate the disease response, all pts received 0.4 mg of etanercept/kg (maximum 25 mg) subcutaneously twice a week for 3 months. After the third month, pts whose conditions had improved according to the definition of Giannini *et al*. (1) entered the second part of the trial, a double-blind study to evaluate the efficacy of etanercept. The pts were randomly assigned to receive either placebo or 0.4 mg/kg of etanercept subcutaneously twice a week (months 4 through 7), until a disease flare occurred or 4 months had elapsed. Efficacy was assessed according to the number of pts with disease flare after etanercept or placebo.

Physical examinations, routine laboratory assessments, and measurements of disease activity were carried out at the beginning and during the course of the study. A final safety assessment was made 30 days after discontinuation of the drug for pts who withdrew from the study or who did not participate in the double blind study, or for pts withdrawing from the study due to a disease flare. At the beginning of the study (months 3 and 7) antinuclear antibodies and antibodies to native DNA, cardiolipin, extractable nuclear antigens and etanercept were evaluated. A response was defined as an improvement of 30% or more (50% and 70 %) in at least 3 of 6 indicators of disease activity [global assessment of the disease severity by the physician, global assessment of overall well-being by the pt or parent, number of "active joints" (joints with swelling, or joints with limitation of motion or pain or both), number of joints with limitation of motion, functional ability, and erythrocyte sedimentation rate], with no more than one indicator worsening by more than 30%. The primary efficacy end-point was the number of pts with disease flare, defined as a worsening of 30% or more in 3/6 variables and a worsening of 30% or more in no more than one of the six variables.

Baseline and demographic characteristics were compared between treatment groups by the Wilcoxon rank-sum test and the likehood-ratio 2-square test. The percentage of pts with a response to therapy who experienced a disease flare while receiving placebo or etanercept in the double-blind study were compared by Mantel-Haenszel methods.

Safety was evaluated by considering the frequency of adverse events, laboratory abnormalities and antibody formation.

**Results:** Sixty-four out of the initial 69 pts (93%) enrolled completed the open label study. The 5 withdrawals were due to urticaria (1 pt), lack of efficacy (2 pts), or refusal of treatment (2 pts). Fifty-one pts (34 females and 17 males) entered the double-blind study. 19 out of the 25 pts assigned to etanercept group (76%) completed the second part of the study; 6 pts withdrew due to disease flare. 7/26 pts in the placebo group (27%) completed the study; 1 was withdrawn by the parents and 18 withdrew due to a disease flare.

At the end of the open-label study, 51/69 pts (74%) met the criteria for improvement. Forty-four (64%) and 25 out of 69 pts (36%), respectively, met the definition of 50% and 70% improvement.

In the double-blind study 21/26 pts who were taking placebo (81%) withdrew because of disease flares, compared with 7/25 pts who received etanercept (28%) ($P = 0.003$). The rates of flare were consistently lower in the etanercept group ($P < 0.001$). The median time to disease flare with placebo was 28 days, as compared with more than 116 days with etanercept ($P < 0.001$).

At the end of the 7-month study 20/25 pts receiving etanercept in the double-blind study (80%) still met the definition of improvement, compared with 9/26 pts of the placebo group (35%, $P < 0.01$). In the etanercept group 18 pts (72%) and 5 pts (19%) met the definition of 50% and 70% improvement, respectively, while in the placebo group 6 pts (23%) and 5 pts (19%) met the definition of 50% and 70% improvement, respectively.

Etanercept was safe and well tolerated. There were no deaths. One pt withdrew due to urticaria and 2 were hospitalized for serious adverse effects (one for depression, one for gastroenteritis-flu syndrome). In the open-label study, the most common adverse events were injection-site reactions, upper respiratory tract infections, headache, rhinitis, abdominal pain, vomiting, pharyngitis, nausea, gastrointestinal infection, and rash. In the double-blind study, there were no significant differences between the two treatment groups in the frequency of adverse effects.

**Conclusions:** Etanercept leads to significant improvement and is safe and well tolerated in active PJRA patients who do not tolerate or do not show an adequate response to MTX. Therefore, etarnecept could be considered as a possible second-line agent for the treatment of PJRA.

### References

1. GIANNINI EH, RUPERTO N, RAVELLI A,LOVELL DJ, FELSON DT, MARTINI A: Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997; 40: 1202-9.

### Comment

*This important study shows for the first time that anti-TNF therapy is highly effective in children with JRA who do not tolerate or who show an inadequate response to methotrexate. These findings are of particular relevance since the list of drugs that have been shown to be effetive in childhood chronic arthritis is small: although anti-TNF agents are not curative – they only suppress disease activity during the period that they are being administered – their use may lead not*

*only to an improvement in the symptoms, but also to the with - drawal of steroids, thus considerably reducing the potential long-term damage due to growth retardation and osteoporo - sis. Of great relevance is also recent evidence that the two available anti-TNF inhibitors – Etanercept and Infliximab (the chimeric monoclonal antibody against TNF- ) – are able to slow or halt the progression of joint damage in adult RA (1,2). Although such studies have not yet been performed in children (and are urgently needed) the excellent results obtained by Lovell et al. suggest that anti-TNF agents may also be able to halt disease progression in children.*

*JRA is a highly heterogeneous condition encompassing dif - ferent forms of chronic arthritis. Lovell's study focused on patients with a polyarticular onset and/or course. It remains to be established in a larger number of patients whether or not anti-TNF treatment is equally effective in patients with other forms of JRA and, in particular, the systemic form; indeed, several studies have suggested that the pattern of cytokine activation is different in systemic JRA with respect to the other onset forms (3). Finally, since TNF is important in the defense against infections and, possibly, cancer, the long-term toxicity of TNF inhibitors remains – in children as in adults – to be established.*

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## References

1. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al*.: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-93.
2. LIPSKYPE, VAN DER HEIJDEDMFM, ST CLAIR EW *et al*.: Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; 343: 1594-602.
3. DE BENEDETTI F, MARTINI A: Is systemic juvenile rheumatoid arthritis an interleukin-6 mediated disease? *J Rheumatol* 1998; 25: 203-7.