Risedronate treatment and extended fracture protection in postmenopausal women

Sir,
I would like to provide some perspective with regard to a published comment (1) on our study of risedronate treatment in postmenopausal women with vertebral fracture (2). The author suggests that risedronate is not effective in reducing vertebral fracture risk after the first year, and that the effects of risedronate “do not compare favorably” with those of alendronate and raloxifene. This assertion is not supported by the data, which show that both risedronate and alendronate produce 3-year vertebral fracture reductions in the range of 40% to 50% in women with baseline vertebral fractures (2-4); the effect of raloxifene 60 mg in a similar population was about 30% (5).

The long-term effects of risedronate on sustaining fracture benefit are now available from a 5-year placebo-controlled study (6). This study demonstrates that the reduction in new vertebral fractures observed in the first 3 years of treatment with risedronate (5 mg daily) is sustained through 5 years. The observed 49% reduction in vertebral fracture risk during the 4th and 5th years of risedronate therapy is quite comparable to the fracture risk reduction observed during the first 3 years of treatment. Consistent results were also observed for risk reduction for non-vertebral fractures.

In his comment, the author also fails to consider the demonstrated efficacy of risedronate in preventing nonvertebral fractures (2, 3, 7); a recent large study found that 3 years of risedronate treatment reduces the risk of hip fracture by 60% in osteoporotic women with baseline vertebral fracture (7). In summary, in contrast to the author’s conclusions, treatment with risedronate 5 mg daily has demonstrated a rapid and sustained fracture efficacy that, together with a favorable safety profile, make it an appropriate first-line option for treatment of women with postmenopausal osteoporosis.

S.T. HARRIS, MD, FACP
University of California at San Francisco
350 Parnassus Avenue, Suite 706
San Francisco, CA 94117-3608, USA

References

Reply

Sir,
We acknowledge receipt of the letter sent by Dr. Harris challenging our appreciation that “the effects of risedronate in osteoporosis do not compare favourably with those of alendronate and raloxifene”. While we fully agree with him that, compared to previous therapies (such as, for example, etidronate), the anti-fracture efficacy shown by risedronate can be of great help for a specific subset of elderly patients, we still have a certain number of reservations about the overall benefit/risk of this medication in the whole population of osteoporotic women.

Regarding the sustained antifracture efficacy of risedronate, we notice that in the only two currently published trials (1, 2) evaluating its anti-fracture efficacy in women with prevalent vertebral fractures, a large fraction of the anti-fracture efficacy observed after 3 years was driven by a significant decrease observed during the first year of treatment. When analysing separately the second and third years of the trials, no significant effect of risedronate compared to placebo was recorded. Dr. Harris refers to a presentation made earlier this year and that would suggest that risedronate could have a sustained anti-fracture efficacy for up to 5 years. To the best of our knowledge, these results have not been yet published in a peer-reviewed journal and therefore were not submitted to the criticisms of the scientific community. Furthermore, this oral presentation reported results obtained in a subset of 255 women at inclusion and 220 women at completion, hence representing only a small fraction of the overall cohort included in the original three-year trials. These results, if published, will subsequently be hardly considered as the demonstration of a sustained efficacy for five years.

Dr. Harris mentioned that consistent results were observed for risk reduction for non-vertebral fractures. Unfortunately, he misquoted our own paper (2) where no significant reduction of non-vertebral fractures (p = 0.06) were observed with risedronate. In its quotation of the large study having discussed the effect of risedronate on the risk of hip fractures in elderly women (3), he is right in stating that risedronate treat-
ment reduces the risk of hip fracture by 60% in osteoporotic women with baseline vertebral fracture. However, this subset of the population only corresponded to 1,128 of the 6,197 patients participating in the whole trial and, while the results of the entire cohort showed a 30% reduction in the relative risk of hip fractures, this reduction was not significant either in women between 70 and 79 years without prevalent vertebral fracture, or in women over the age of 80 with at least one clinical risk factor for hip fracture. Therefore, we do not share his appreciation that the efficacy of risedronate in preventing non-vertebral fractures has been consistently shown throughout various studies.

Further on Dr. Harris mentioned that risedronate has “a favourable safety profile”. While the gastro-intestinal safety of this compound appears to be in the same range as that observed with other bisphosphonates like alendronate, it should not be ignored that the prolonged use of risedronate in women with established osteoporosis has been repeatedly linked with a statistically significant increase in the occurrence of pulmonary cancer (3.9/1,000 patients-year of exposure and 1.9/1,000 patients-year of exposure for 2.5 and 5 mg/day, respectively, compared to 1.2/1,000 patients-year of exposure with placebo, based on the results of ten phase III studies involving approximately 30,000 patients-year of exposure) (4). The European and American Regulatory authorities, following the opinion of an expert panel, concluded that a causal association between risedronate use and lung cancer was highly improbable. However, these figures should be appropriately taken into account when evaluating the overall risk/benefit ratio of this bisphophonate, particularly when other bisphosphonates do not show this statistically significant increase in lung cancer.

In conclusion, we agree with Dr. Harris that risedronate at the dose of 5 mg/day has been consistently shown to significantly reduce vertebral fractures. However, from the currently published data, no evidence exists that this reduction is actually sustained for more than one year. Since this dosage of risedronate did reduce non-vertebral fractures in the North American study (1), but not in the European trial (2) and since the reduction of hip fractures was mainly seen in a subset of the hip fracture trial corresponding to less than 20% of the overall population, we cannot endorse the assumption that consistancy has been shown in the non-vertebral fracture efficacy of risedronate. Eventually, taking into account the lung cancer issue reported throughout the phase III trials with this compound, we maintain our initial position that risedronate use should be mainly considered for patients who did not properly respond to more efficient and/or safer medications like alendronate or raloxifene.

J.Y. REGINSTER, MD, PhD
Bone and Cartilage Metabolism Unit
University of Liège, 45 Quai Godofroid Kurth
4020 Liege, Belgium

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Etanercept improves rheumatoid arthritis partially responsive to methotrexate

Authors: M.E. Weinblatt et al.

Title: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate


Aim: Methotrexate (MTX) is currently the drug of first choice in rheumatoid arthritis (RA), but may result in only the partial relief of symptoms. A 24-week, double-blind trial was conducted to test whether the combination of MTX with etanercept, a soluble tumor necrosis factor receptor (p75):Fc fusion protein, could provide additional benefit to RA patients (pts) only partially responsive to MTX alone.

Methods: 89 RA pts (75 females and 14 males) with active disease despite at least 6 months of MTX therapy at a stable dose of 15-25 mg per week were enrolled in the study. At baseline the pts had a mean RA duration of 13 years, and a median of 28 tender and 18 swollen joints. 59 and 30 pts respectively were randomly assigned to receive etanercept+MTX or placebo+MTX. The mean weekly dose of MTX per pt was 19 mg in the first and 18 mg in the second group. As an adjunct to MTX, etanarcept (25 mg/dose) or placebo was administered subcutaneously twice weekly. Pts taking non-steroidal anti-inflammatory drugs and/or prednisone not exceeding 10 mg daily were eligible if the doses had been stable for at least 4 weeks before the beginning of the study and remained stable during the study period.

Physical examinations, routine laboratory assessments, and autoantibodies tests (including autoantibodies to etanercept) were conducted at the beginning and during the course of the study. Measures of disease activity included evaluations of 71 joints for tenderness, 68 joints for swelling, the physician’s and patient’s global assessment of disease, the patient’s assessment of pain on a visual analogue scale, the patient’s assessment of disability according to the health assessment questionnaire (HAQ), the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values. Adverse events, changes in laboratory values, and withdrawal were also evaluated.

The primary efficacy endpoint was the proportion of pts meeting the ACR preliminary criteria for improvement in RA (ACR 20) at 24 weeks. Pts had to show a reduction of at least 20% in the number of swollen and tender joints and an improvement in at least 3 of the following items: the patient’s
assessment of pain, the physician’s and patient’s global assessment of disease, the patient’s assessment of disability according to the HAQ, and the values for acute phase reactants (either ESR or CRP). Other efficacy endpoints were the proportion of pts meeting the ACR 20 criterion at 12 weeks, the ACR 50 and ACR 70 criteria (an improvement in the same variables by 50% and 70%, respectively) at 12 and 24 weeks, and the percent of pts showing improvement in individual measures of disease activity at 12 and 24 weeks. Safety was evaluated based on the frequency of adverse events, laboratory abnormalities and antibody formation. ACR 20 and ACR 50 response rates were compared using the chi-square test. The two-tailed Fisher’s exact test was used for the ACR 70 response rates and for the data on safety.

**Results:** 57 of the 59 pts receiving etanercept plus MTX completed the study; 2 withdrew due to adverse effects unrelated to etanercept. Six of the 30 pts taking placebo plus MTX group withdrew: 4 due to lack of efficacy and 1 due to myocardial infarction; one pt. was lost to follow up. The etanercept plus MTX group showed significantly superior outcomes for all the endpoints considered. In particular, the primary efficacy endpoint – ACR 20 at 24 weeks – was achieved in 71% of the pts compared with 27% in the placebo plus MTX group (P < 0.001). 39% of the pts receiving etanercept plus MTX and 3% receiving placebo plus MTX met the ACR 50 criteria at 24 weeks, while 42% pts in the first group and 0% in the second group met the same criteria at 12 weeks (P < 0.001 in both cases). ACR 70 criteria were reached by 15% of the pts in the first group and by no patient in the second group (P= 0.03). At 12 and 24 weeks all of the individual activity indexes were significantly improved in the group receiving etanercept plus MTX compared to the group receiving placebo plus MTX.

Etanercept was well tolerated; the only adverse events that were significantly higher with respect to placebo were mild reactions at the injection site. Most of these resolved without treatment and none required discontinuation of the drug. No patient withdrew from the study because of adverse etanercept-related effects.

**Conclusions:** The addition of etanercept to MTX is effective in improving RA that is persistently active despite MTX therapy. The association is safe, well tolerated, and could be useful for the treatment of RA cases that are refractory to traditional therapies.

**Comment**

The treatment protocol presented by Weinblatt more than two years ago represents at the present time one of the most widely accepted and satisfying combination therapies for rheumatoid arthritis (RA). The use of TNF- blockers remains in my opinion the best and fastest way to treat acute and severe inflammatory reactions, including synovitis, in RA. However, concerning the sustained administration of TNF-blockers in chronic inflammation, some doubts have been raised regarding the appearance of concomitant chronic infections (i.e. TBC). The risk of infection in RA is of course increased by combination therapy with immunosuppressive drugs (i.e. cyclosporine, leflunomide, methotrexate, etc.). Since TNF- is one of the major – but not the only – mediators of acute and chronic inflammation, at least in RA, it is not sufficient to treat the patient for months with TNF-blockers alone to control the progression of the disease. The association of TNF- blockers and methotrexate seems to modulate some of the mechanisms involved in the inflammatory reaction (1). In certain cases methotrexate appears to potentiate the antiinflammatory effects of the TNF- blockers. For example, it has been shown that adenosine, whose production is increased by methotrexate, inhibits TNF-expression in a monocytes cell line and that monocytes release adenosine after treatment with MTX (2). In addition, recent investigations have shown both a late up-regulation of soluble TNF- receptor (sTNFR p75) synthesis by PBMC after 24 hours of MTX treatment, and the MTX-induced increase of sTNFR p75 from cultured monoblastic leukemia cells, suggesting a further antiinflammatory mechanism through the inhibition of the effects of TNF- (3, 4). Therefore, since different mediators are involved in RA joint destruction, combination therapies are essential, including the use of low dose corticosteroids to control the complex pathways that are at work (4). Naturally, over time the effects of the combination therapies themselves will induce a progressive reduction in serum TNF- levels that should not be depleted in the human body by the further and excessive administration of TNF- blockers. In this regard, the subcutaneous administration of the soluble receptor (etanercept) seems to exert its effects in a less acute manner than the intravenous administration of monoclonal antibody (infliximab).

In conclusion, the association of a TNF- blocker and methotrexate as proposed by the study of Weinblatt, one of the first rheumatologists to introduce the use of low-dose methotrexate in the treatment of RA, seems to be one of the most acceptable combination therapies for the disease (5). However, the timing for the long-term administration of TNF- blockers in chronic diseases such as RA must be further studied in order to optimize the ratio of efficacy to adverse events.

M. CUTOLO, MD
Dept. of Internal Medicine and Medical Specialties
University of Genova, Viale Benedetto XV no. 6
16132 Genova, Italy

**References**