Atrial Fibrillation and Zolendronic Acid in Paget's Disease

To the Editor: The HORIZON[1] study was recently published in the *New England Journal of Medicine.* It is an international, multicentric, randomized, double blind and controlled trial in which the efficacy and safety of a yearly intravenous administration of 5 mg of zolendronic acid for postmenopausal osteoporosis is tested. This study included a total of 7765 patients.

The efficacy study proved that after 3 years there was a reduction of 70% in vertebral fractures, of 41% in hip fractures, and 25% in on-vertebral fractures in the group of patients who were treated with zolendronic acid; the efficacy of the drug with respect to the placebo was therefore demonstrated in fracture reduction.

The safety part of the study showed a larger number of reactions in the treatment group compared to the placebo group. All of these reactions appeared in the 3 days that followed the administration of the drug and all o them were mild adverse events that included: cold-like symptoms, fever, muscle pain, headache, and joint pain. A mild, transient descent in the serum calcium concentration was seen in the treatment group. The incidence of osteonecrosis of the jaw was similar in both groups with 1 case reported in both.

In a surprising way, an increase in the incidence of arrythmia was detected in the treatment group with respect to the control group (6.9% vs 5,3%; *P*=.003). In 1.3% (50 patients) of the treatment group these arrythmias were manifested in the form of severe atrial fibrillation compared to 0.5% (20 patients) in the placebo group (*P*<.001). In the treatment group, 47 of the 50 cases of severe atrial fibrillation appeared 30 days after the administration of the drug. Among the patients who completed 3 years of treatment, a subgroup was selected prior to the study in which an electrocardiogram was performed, without noticing differences in the prevalence of atrial fibrillation between the 2 groups.

The cause originating the appearance of this atrial fibrillation is unknown. The transient and mild reduction in serum calcium levels is not considered to be the cause of the process. This adverse event appears 30 days after the administration of the drug, but during that period serum concentration of the drug is almost imperceptible. This has been noted before, in 1997, during the Fracture Intervention Trial (FIT),[2] a study that compared the efficacy of oral alendronate versus placebo for the treatment of postmenopausal osteoporosis in 6459 women. This study had already observed a higher incidence of severe atrial fibrillation in patients receiving alendronate (1.5%) versus patients receiving placebo (1%) during the 4 years the study lasted.

In September 2005, Reid et al[3] published in the *New England Journal of Medicine* a double blind, randomized, 6 month long trial in which the efficacy of zolendronic acid compared to risedronate for the control of bone exchange of Paget's disease was measured. A single intravenous infusion of zolendronic acid was compared to oral risedronate at a dose of 30 mg/day during 60 days, and a larger therapeutic response (defined as a normalization of the concentration of alkaline phosphatases or a reduction of at least 75% in the total excess of alkaline phosphatases) in the group treated with zolendronic acid (96% vs 74.3% of the patients treated with risedronate). A faster, longer duration therapeutic response was seen in the group of patients with Paget's disease treated with zolendronic acid.

This trial observed a larger rate of adverse events in the group of patients treated with zolendronic acid. Most of these adverse events appeared in the first 3 days after the infusion and were described as cold-like symptoms of a mild-to-moderate intensity. A larger rate of hypocalcemia was also seen in the group of patients treated with zolendronic acid. No cardiac events were described in this study.[3]

Recently, Hosking et al[4] have published a study comparing the capacity of zolendronic acid of maintaining long-term control of bone exchange, compared to risedronic acid and show a larger efficacy of zolendronic acid in the 2 years of treatment. This study did not describe the appearance of cardiac rhythm alterations either.

On September 17, 2007, the online version of *The New England Journal of Medicine* published a double blind, placebo-controlled, randomized trial in which zolendronic acid was administered at a dose of 5 mg versus the a random allocation of placebo, to patients who had suffered a hip fracture. Treatment was administered in the 90 days following hip surgery and repeated every 12 months. In this study there was a reduction of 35% in the risk of new fractures in the group of patients treated with zolendronic acid compared to the placebo group. In the zolendronic acid group there was a higher frequency of bone and joint pain as well as fever; however, there were no statistically significant differences between the 2 groups with respect to the appearance of atrial fibrillation. No cases of jaw osteonecrosis were seen.[5]

We do not know of any case of severe atrial fibrillation described in patients with Paget's disease treated with zolendronic acid; however, in January 2007, a patient diagnosed as Paget's disease, undergoing treatment with 5 mg of zolendronic acid for the control of his illness, came to the hospital due to a severe atrial fibrillation which had presented 30 days after administration of the drug. Because of this severe adverse event, the department of rheumatology of the Hospital San Rafael in Barcelona has included the performance of an electrocardiogram as part of the study protocol before the first infusion and at months

1, 3, 6, 12, and 18 after the infusion to patients with Paget's disease who receive treatment with zolendronic acid.

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