INTRODUCTION: No effective non-operative treatments are available for Perthes disease. We have previously reported significant improvement in outcome in traumatic osteonecrosis in growing rats by intervention with zoledronic acid (ZA), a potent third generation bisphosphonate. In this study we examine the effect of ZA on a model of spontaneous osteonecrosis in growing rats. We hypothesized that administration of ZA could favorably alter femoral head shape by preserving architecture while allowing bone repair to proceed.

METHODS: A model of spontaneous osteonecrosis was utilized in 120 male spontaneously hypertensive rats (SHR). Animal ethics approval was received (WAEC-103.06-02). Approximately 50% of SHR rats develop osteonecrosis in the first 15 weeks of life, resulting in femoral head deformity similar to Perthes disease. 120 4-week old rats were divided into three dosing groups of 40, each group received either saline monthly, 0.05 mg/kg ZA monthly for 3 doses, or 0.015 mg/kg ZA weekly for 10 doses. The same total dose was given to active groups.

Rats were housed in cages that encouraged standing erect on hind limbs, which has been shown to increase femoral head deformity. Following euthanasia at 15 weeks of age, high-resolution Faxitron radiographs were taken and enlarged X 12 to enable blinded Mose circle analysis of femoral head sphericity by two different observers. Interobserver agreement for rating sphericity of heads was substantial with kappa = 0.75. A modified epiphyseal quotient (height/width) and maximum epiphyseal height was also measured by a different blinded observer.

The femoral heads of 96 rats (192 heads) were decalcified in 0.5% paraformaldehyde/14.5% EDTA, central coronal sections were cut at 5 microns and stained with H&E. The remaining femoral heads (48) were processed undecalcified, embedded in methylmethacrylate resin and microscopic analysis. DXA scans for BMD and BMC were analyzed in consecutive sections stained with Von Kossa or used for fluorescent microscopic analysis. Standard histomorphometric techniques were used for analysis. ANOVA or unpaired t tests were used for parametric data and chi square analysis for proportions.

RESULTS: 53% of control femoral heads showed radiographic signs of osteonecrosis, in line with other reports on this model. In ZA treated groups, radiographs revealed less osteopenia and improved sphericity of the femoral heads (Fig 1). There was minimal or no difference between the two treatment regimens for the factors analysed, but both treatment groups and the pooled treatment results were significantly different from saline controls.

Histological observations revealed that in ZA treated rats in which the ossific nucleus had formed, there was minimal resorption, with new bone forming on the old necrotic trabeculae, whereas in controls resorption was leading to collapse (Fig 3).

Histomorphometry on undecalcified specimens documented a mean 42% increase in trabecular number in treated groups (p<0.01), while trabecular thickness was 22% higher in controls (p<0.01). There was a net increase of 11% in bone volume (BV/TV) in treated animals (p=0.02). There was a mean 2.5% negative effect on longitudinal growth of the femoral shaft in treated animals as a result of the ZA therapy.

DISCUSSION: We have previously reported that zoledronic acid can prevent epiphyseal collapse in a traumatic model of osteonecrosis in growing rats. This study confirms that in spontaneous osteonecrosis, ZA can also improve outcome. The histomorphometric data can be interpreted that by preserving a high number of trabeculae, the BV/TV and BMD were increased, leading to better resistance to deformation. The increase in the thickness of the remaining trabeculae in untreated rats was not sufficient to compensate for decreased trabecular number and maintain femoral head shape. Grossly thickened trabeculae have been noted in human pathological specimens of Perthes disease. Longer term follow up in this model may provide further information about the final remodeled shape of the femoral head at maturity. Further supportive evidence could provide the basis for clinical trials aimed at prevention of epiphyseal collapse in Perthes disease.

REFERENCES:

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