TRABECULAR BONE TURNOVER IS RE-ESTABLISHED SOONER IN OVARIECTOMIZED RATS TREATED WITH RISEDRONATE COMPARED TO ALENDRONATE

INTRODUCTION
Risedronate (RIS) and alendronate (ALN) are nitrogen-containing bisphosphonates approved in the US for the treatment and prevention of osteoporosis. Bisphosphonates reduce bone loss due to estrogen-deficiency by inducing osteoclast apoptosis to decrease bone turnover. Data from numerous clinical trials conducted over the past ten years demonstrate that ALN and RIS are efficacious in reducing post-menopausal bone loss, yet it remains unclear how long the benefits of treatment are maintained after stopping treatment. While there are no head-to-head trials which specifically compare the effects of discontinuing ALN and RIS therapy, data from clinical trials suggest that the suppression of bone turnover is maintained longer in patients treated with ALN than RIS [1-6].

Pharmacokinetic studies in animals and humans advocate that ALN has a longer terminal half-life than RIS [7-10]. Given the potentially longer skeletal half-life of ALN, re-establishment of normal rates of bone remodeling may take longer following its withdrawal than with an equivalent dose of RIS. The aim of this study was to investigate the skeletal response to the withdrawal of RIS and ALN using an ovariectomized (ovx) animal model. We hypothesized that normal bone turnover rates would be re-established sooner following the withdrawal of bisphosphonate therapy in ovx rats treated with RIS than in those treated dose-equivalently with ALN.

MATERIALS AND METHODS
Experimental animals: Two hundred and ten six-month old female Sprague-Dawley rats weighing ~300g were obtained from Harlan Laboratories (Indianapolis, IN). Rats were pair-housed in plastic cages and fed a standard diet. All procedures performed in this experiment were in accordance with the Animal Care and Use Committee guidelines.

Treatment: Rats were ovx at six-months of age and starting six weeks post-ovx were randomized into one of four treatment groups: vehicle-treated controls (CON; 0.3 ml saline), alendronate (ALN; 2.4 µg/kg), low-dose risedronate (RISlow; 1.2 µg/kg), or high-dose risedronate (RIShigh; 2.4 µg/kg) via subcutaneous injection. Rats were treated three times per week for eight weeks, after which 10 rats per treatment group were sacrificed at 0, 4, 8, 12 and 16 wks after stopping treatment. Ten rats served as baseline ovx controls. Doses of ALN and RIS were based on clinical dose levels (on an oral mg/kg basis) and on doses known to inhibit bone loss in ovx rats. From a clinical perspective, 1 remodeling cycle is equal to ~1 month in rats and ~4-6 months in humans. Fluorochrome label (calcine) was administered 10 and 4 days prior to sacrificing for histological measurements.

Measurements: Histomorphometry was performed on the metaphysis (trabecular region) and mid-shaft (cortical region) of the tibia. Unstained sections were examined for mineral apposition rate (MAR; µm/day), bone formation rate (BFR/BS; µm²/µm²/year) and mineralizing surface (MS). In addition, bone mineral density (BMD; g/cm²) of the distal femur was assessed by dual-energy x-ray absorptiometry (DXA).

RESULTS
Treatment effects: Indices of bone turnover were significantly suppressed in all drug treated groups compared to vehicle-treated CON after 8 wks of treatment (P<0.05), and BMD of the distal femur increased significantly in all drug treated groups after 8 wks of treatment compared to vehicle-treated CON (P<0.05) (Figure 1A-C).

Withdrawal effects for the proximal tibia metaphysis: Trabecular bone turnover in the RISlow and RIShigh groups increased steadily following the withdrawal of treatment. In contrast, trabecular bone turnover in the ALN treated groups did not demonstrate increases in bone turnover at any time point during treatment withdrawal. The ALN treated groups remained significantly lower than vehicle treated CON at all time points (P<0.05). At 16 wks the RIS treated groups were not significantly different from vehicle-treated CON (P>0.05) and there were no significant differences between the drug-treated groups. (P>0.05) (Figure 1A).

Withdrawing effects for the tibia mid-shaft: After 8 wks of treatment, BFR/BS was significantly reduced on the endocortical surface in all drug treated groups compared to vehicle-treated CON (P<0.05). Within as little as 4 wks, and continuing through 16 wks of treatment withdrawal there were no significant differences among the drug-treated groups or vehicle-treated CON for endocortical BFR/BS (all P>0.05) (Figure 1B).

Withdrawal effects for the distal femur: BMD began to decline in all drug treated groups as early as 4 wks, but remained significantly higher than controls until 16 wks (all P<0.05). By 16 wks, there were no significant differences between vehicle-treated CON and all drug-treated groups for BMD (P>0.05) (Figure 1C).

DISCUSSION
Normal trabecular bone turnover is re-established sooner in animals treated with RIS compared to ALN. Specifically, bone formation rates remained significantly lower in trabecular bone of the proximal tibia in ALN treated animals than non-treated controls through 16 wks after stopping treatment, while those treated with either dose of RIS demonstrated a gradual recovery of normal bone formation rates. In contrast, on the endocortical surface of the tibia mid-shaft, bone turnover rates in all drug treated groups increased significantly as soon as 4 wks, and continued to increase up to 16 wks of treatment withdrawal. Outcomes from this study may have important implications for designing effective therapies for the treatment and prevention of osteoporosis.

REFERENCES

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