BONE

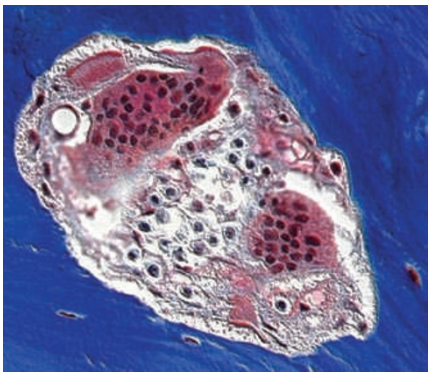
Giant osteoclasts detected in bone biopsy samples after alendronate therapy

Long-term treatment with the oral bisphosphonate alendronate increases the number of osteoclasts and can lead to formation of giant osteoclasts, according to Robert S. Weinstein of the University of Arkansas for Medical Sciences (UAMS), Little Rock, AR.

Nitrogen-containing (amino) bisphosphonates, such as alendronate, are widely used to prevent or treat osteoporosis. This class of drugs slows bone resorption and thereby increases BMD; however, the precise effect of bisphosphonate therapy on the target cell—the osteoclast—remains elusive. As bisphosphonates promote osteoclast apoptosis, one line of thought states that bisphosphonate therapy decreases the total number of osteoclasts. Dr Weinstein, a Professor of Medicine at UAMS, disputes this hypothesis.

In May 2006, Weinstein identified an unexpected osteoclast-like cell type in a bone biopsy specimen from a patient who had received amino bisphosphonate therapy. The morphology of the cell type detected bore a striking resemblance to that of cells he had previously observed in histological bone samples taken during his collaboration with Michael McClung (Oregon Osteoporosis Center, Portland, OR) in 1994 on the use of alendronate as a preventative therapy for postmenopausal osteoporosis. Weinstein was able to review his original laboratory notes from that study and found that many of the histological specimens contained giant osteoclast-like cells. Armed with this information, Weinstein decided to re-evaluate the bone histomorphometry of the biopsies collected by McClung and coworkers.

The McClung study was a 3-year, multicenter, double-blind, randomized, placebo-controlled trial that enrolled 447 healthy, postmenopausal women aged 40–59 years. The investigators assigned the women to one of five interventions:



Permission obtained from R. S. Weinstein

alendronate 1, 5 or 10 mg daily for 3 years, alendronate 20 mg daily for 2 years followed by 1 year of placebo or 3 years of placebo. The study found that treatment with alendronate increased BMD from baseline. Transiliac bone biopsy specimens taken after 3 years of treatment were available from 55 women; tetracycline labeling was performed to assess bone mineralization. Longitudinal, formalin-fixed, methylmethacrylate-embedded sections were cut with freshly sharpened blades to prevent artifacts and cover slips were weighted to achieve the best possible planar sections. Sections were stained to assess nuclear morphology or left unstained to assess tetracycline labeling. Additional sections were stained for the presence of the osteoclast marker, tartrate-resistant acid phosphatase (TRAP). Apoptosis was assessed by *in situ* end-labeling.

Contrary to popular belief, Weinstein *et al.* found a 2.6-fold increase, rather than a decrease, in total osteoclast numbers after treatment with 10 mg alendronate daily for a 3-year period. Moreover, the total number of osteoclasts detected correlated with increasing dose of alendronate. Of particular interest, treatment with alendronate led to the formation of an excessively nucleated, apoptotic, TRAP-positive cell type that was detached from the bone surface. These giant osteoclasts represented 27% of the total osteoclast number in the group treated with 10 mg alendronate. Giant osteoclasts were not detected in bone samples from women who had received placebo for 3 years; however, such cells were still present in samples taken from women who discontinued alendronate therapy 1 year previously.

The results of this study have a number of implications. The presence of giant osteoclasts could lead to mistaken diagnoses of bone disorders other than osteoporosis and cause unnecessary additional laboratory testing or referrals. Joan Marini, Chief of the Bone and Extracellular Matrix Branch of the National Institute of Child Health and Human Development, points out that 2–3 years of alendronate therapy is no longer considered long-term treatment in adults. Nevertheless, "...data from osteoporotic adults should make us especially cautious when using more potent amino bisphosphonates, such as pamidronate, in children," says Marini. "Given the decade-plus persistence of amino bisphosphonates in bone, Weinstein *et al.* add fuel to the argument for limiting the duration and cumulative dose administered to children with various causes of genetic and secondary osteoporosis."

The next step for Weinstein is to evaluate the biology of the giant osteoclast. "Do these giant cells secrete anything that could potentially be of harm to the patients?" he asks. Furthermore, "...what happens when patients with glucocorticoid-induced osteoporosis are treated with bisphosphonates? Are the giant cells present in greater numbers or size?" Weinstein's observations clearly raise important questions about the long-term effects of bisphosphonate therapy on osteoclast function.

Vicky Heath

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