

COMMENTARIES

Should We Be Concerned About Giant Osteoclasts?

Robert R. Recker

Creighton University School of Medicine, Omaha, Nebraska, USA

Commentary on: Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. *N Engl J Med.* 2009 Jan 1;360(1):53-62.

Since the introduction of alendronate in 1995, aminobisphosphonates have become the most widely used therapy for osteoporosis. They are potent inhibitors of bone resorption, and clinical trials demonstrate increases in bone mass, a reduction in indices of bone resorption and a reduction in fractures. Early on, investigators were surprised that osteoclasts did not disappear during treatment (1). In fact, their numbers were actually increased (1;2). Now, 14 years after the introduction of aminobisphosphonates, another osteoclast surprise is reported by Weinstein *et al.* (3) who find that not only are osteoclast numbers increased 2.6-fold, but also that there seems to be a cumulative, dose-related increase in osteoclast size and numbers of nuclei, with many showing features of apoptosis (the authors did not specify whether all, or a portion, of the nuclei in the giant osteoclasts were apoptotic). What is the significance of this finding? Are these cells innocently lingering in areas close to trabecular surfaces (the authors did not report seeing them in cortices of iliac biopsies)?

The osteoclasts that Weinstein *et al.* describe (3) are giant, hypernucleated, pyknotic, fragmented, and apoptotic, occurring in 27% of patients treated with alendronate, 10 mg/d, for three years. These cells exhibit other unique morphologic features such as shallow resorption cavities, loss of ruffled border and separation from bone surfaces. The authors also found greater numbers of normal-appearing osteoclasts in these same specimens.

The authors suggest that the mechanism creating the large, multinucleated osteoclasts is inhibition of farnesyl pyrophosphate synthase, with resultant disruption of the ruffled border, and loss of the sealed boundary around the resorption site. This would result in loss of acid-dependent calcium release from the bone matrix, reducing extracellular calcium availability in the area of the osteoclast. Since the extracellular calcium normally released by osteoclast work is the signal for osteoclast death, the osteoclasts linger and accumulate more nuclei by continued fusion with mononuclear precursors. Some, or all, of those nuclei ultimately become apoptotic, but the cells resist ingestion by macrophages, and thus linger in the area. This effect is long-lasting since the abnormal, large osteoclasts were present even a year after the bisphosphonate was discontinued in those treated for two years then left untreated for another year before iliac biopsy. This lingering effect one year after discontinuing alendronate could be due to the long residence time, and continued release, of the bisphosphonate that accumulated in the bone tissue. However, osteoclast function returned in that year off treatment, suggesting that the phenomenon is not due to continued exposure to bisphosphonate from prior accumulation.

The authors suggest evidence in favor of their hypothesis from patients with Albers-Schönberg disease (marble bone disease) that is caused by a mutation in the gene encoding a chloride channel, thus preventing production of acid under the ruffled border of osteoclasts (4). These patients develop large, multinucleated osteoclasts, perhaps because of a lack of the calcium ions needed to signal apoptosis

(5). It is unclear whether there is a fraction of these accumulated nuclei that are apoptotic. The authors also point to the large multinucleated osteoclasts in Paget's disease as possibly another example of this phenomenon.

Are these osteoclasts a menace? Thus far there does not seem to be toxicity associated with accumulation of these overblown osteoclasts. However, since they seem to linger for a very long time, and their numbers seem to accumulate with longer treatment and greater cumulative dose, they cannot be ignored. Some questions: How long can they accumulate, and can they accumulate to the extent that marrow elements are crowded? Probably not, since during three years of bisphosphonate exposure they came to occupy no more than a trivial volume of the marrow space. Is there any potential for tumor transformation? Again, probably not, since the apoptotic nuclei would have little or no capacity for transformation. Furthermore, it is reassuring that there is no evidence of toxicity of these cells in our clinical experience with long-term bisphosphonate treatment in patients well in excess of 10 years (6;7). Stay tuned!

Conflict of Interest: The author reports that he is a consultant for Merck, Pfizer, Wyeth, P&G, Amgen, Novartis, Roche, and Lilly.

Peer Review: This article has been peer-reviewed.

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