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The cathepsin K inhibitor AAE581 induces morphological changes in osteoclasts of treated patients

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Titre	The cathepsin K inhibitor AAE581 induces morphological changes in osteoclasts of treated patients
Type de publication	Article de revue
Auteur	Chappard, Daniel [1], Marchand-Libouban, Hélène [2], Mindeholm, Linda [3], Baslé, Michel-Félix [4], Legrand, Erick [5], Audran, Maurice [6]
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Résumé en anglais	Inhibitors of Cathepsin K (Cat-K) are recognized as an interesting way to inhibit osteoclast (OC) activity. OCs from patients treated with the anticathepsin-K inhibitor AAE581 (balicatib) were found enlarged. They contained numerous vacuoles filled with tartrate resistant acid phosphatase (TRAcP), an intracellular enzyme that terminates the degradation of collagen internalized in OC transcytotic vesicles. In a phase 2 clinical study, 675 patients with postmenopausal osteoporosis received the Cat-K inhibitor AAE581 at 0, 5, 10, 25, or 50 mg/D during 1 year. Eleven patients had a transiliac bone biopsy, studied undecalcified. Histoenzymatic detection of TRAcP was used to identify and count OC number. The histomorphometrist was not aware of the randomization of patients at the time of analysis. OC were unstained in one patient because of a failure in the fixation protocol, but easily observable in the 10 remaining patients. Whatever the received dose, treated patients exhibited a characteristic aspect of the OC cytoplasm which appeared filled of deeply-stained brown vacuoles, making cells looking like bunches of grape. These round vacuoles, evidenced on TRAcP-stained sections, were due to the accumulation of intracytoplasmic TRAcP. This led to a moderate enlargement of the OC size when compared to a series of control osteoporotic patients. AAE581 did not induce OC apoptosis at any dosage but it modified OC morphology. Cat-K inhibition (inhibiting the extracellular collagen breakdown) is associated with a compensatory accumulation of intracellular TRAcP that could not be used to complete protein degradation. TRAcP is also known to be degraded by Cat-K. Microsc. Res. Tech., 2010.

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