Effects of zoledronic acid on senescence and SASP markers

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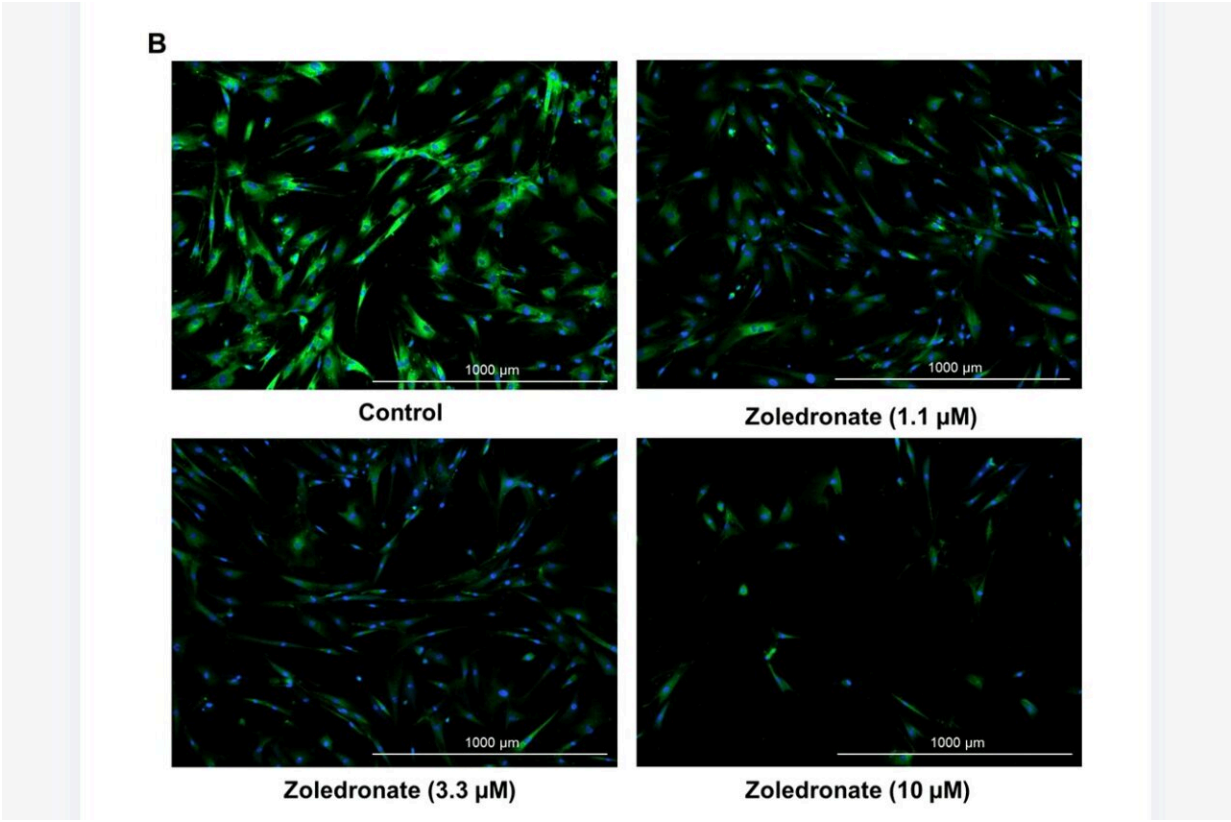

Zoledronic acid has senolytic effects in human lung fibroblast IMR90 cells. Credit: 2023 Samakkarnthai et al.

A new research paper, titled "In vitro and in vivo effects of zoledronic acid on senescence and senescence-associated secretory phenotype

markers," was published on the cover of *Aging*

Zoledronic acid has been found to reduce fracture risk and, in some studies, to decrease mortality in humans and extend lifespan and healthspan in animals. Because senescent cells accumulate with aging and contribute to multiple comorbidities, the non-skeletal actions of zoledronic acid could be due to senolytic (killing of senescent cells) or senomorphic (inhibition of the secretion of the senescence-associated secretory phenotype (SASP)) actions.

In this new study, researchers from the Mayo Clinic, Phramongkutklao Hospital and College of Medicine, Eberhard Karls University, University of Minnesota, University of Oxford, and University of Sheffield tested the above hypothesis using multiple complementary approaches (in vitro, in vivo, and in silico) to evaluate possible effects of zoledronic acid on modulating cellular senescence.

The researchers first performed in vitro senescence assays using human lung fibroblasts and DNA repair-deficient mouse embryonic fibroblasts, which demonstrated that zoledronic acid killed senescent cells with minimal effects on non-senescent cells. Next, in aged mice treated with zoledronic acid or vehicle for 8 weeks, zoledronic acid significantly reduced circulating SASP factors, including CCL7, IL-1β, TNFRSF1A, and TGFβ1 and improved grip strength. Analysis of publicly available RNAseq data from CD115+ (CSF1R/c-fms+) pre-osteoclastic cells isolated from mice treated with zoledronic acid demonstrated a significant downregulation of senescence/SASP genes (SenMayo).

To establish that these cells are potential senolytic/senomorphic targets of zoledronic acid, the team used single cell proteomic analysis (cytometry by time of flight [CyTOF]) and demonstrated that zoledronic acid significantly reduced the number of pre-osteoclastic (CD115+/CD3e-/Ly6G-/CD45R-) cells and decreased protein levels of

p16, p21, and SASP markers in these cells without affecting other immune cell populations.

The researchers conclude, "Collectively, our findings demonstrate that zoledronic acid has senolytic effects in vitro and modulates senescence/SASP biomarkers in vivo. These data point to the need for additional studies testing zoledronic acid and/or other bisphosphonate derivatives for senotherapeutic efficacy."

More information: Parinya Samakkarnthai et al, In vitro and in vivo effects of zoledronic acid on senescence and senescence-associated secretory phenotype markers, *Aging* (2023). DOI: 10.18632/aging.204701

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