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Nitric Oxide-mediated cytotoxic effect induced by zoledronic acid treatment on Human Gingival Fibroblasts

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Zoledronic acid (ZA) belongs to bisphosphonates (BPs), drugs administered to treat resorptive bone diseases. Although ZA is largely used in the clinical practice, significant adverse effects of ZA, such as osteonecrosis of the jaw (ONJ), were recorded.

The aim of this work was to evaluate the role of Nitric Oxide (NO) in the *in vitro* response of Human Gingival Fibroblasts (HGFs) to 1, 5, 10 and 100μM ZA.

HGFs morphology was evaluated through phase contrast microscopy and live/dead staining; MTT and ELISA assays were applied to measure cell viability, Collagen Type I and IL6 secretion. ROS production and mitochondrial membrane potential were evaluated by flow cytometry; NO production and NOS activity by spectrophotometric analysis; eNOS and nNOS expression by fluorescence microscopy.

Viable fibroblasts are evidenced in control sample while floating dead cells and cells close to detachment phase in ZA treated sample along with decreased level of Collagen Type I. Control sample shows higher number of viable cells respect to ZA treated one and ROS production increases when ZA is added. Released NO in ZA treated sample appears higher and NO overproduction is related to increased nNOS activity. IL 6 secretion level is higher in ZA treated sample than in control one.

Our results suggest ROS involvement in NO overproduction, due to nNOS recruitment, both at low and high doses. In turn, NO release seems to be able to trigger the inflammatory response only when high doses are administered.