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In vitro comparison of new bisphosphonic acids and zoledronate effects on human gingival fibroblasts viability, inflammation and matrix turnover

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Bisphosphonates (BPs) are well known clinically used drugs, commonly applied to treat osteoclast-mediated bone resorption. Some clinically used BPs were demonstrated to be able to inhibit the activity of matrix metalloproteinases (MMPs) (1), a protease family required to fully degrade all the components of the extracellular matrix during connective tissue remodelling (2). Combining the arylsulfonamide function with the bisphosphonic group, several compounds were synthesized to obtain selective inhibitors of MMPs. The aim of the present work is to compare the effects on cell adhesion, cytotoxicity, inflammatory response occurrence and matrix turnover process in an in vitro model of primary human gingival fibroblasts (HGFs) treated with newly synthesized sulfonamide BPs and with zoledronic acid (ZA), a clinically used drug. Western blot was used to measure Procollagen I, β1 integrin MMP-8 and MMP-9, phase contrast and MTT for cell viability, LDH was performed for toxicity evaluation, ELISA for Prostaglandin E2 (PGE2) secretion assessment. When compared with ZA, the treatment with the newly synthetized compounds shows increasing viability, Procollagen I expression and decreased expression of β1 integrin in HGFs. Higher levels of released LDH, PGE2 and MMP-9 expression are recorded in ZA-treated HGFs. Increased levels of MMP-8 are recorded in newly synthetized compounds-treated samples.These findings imply that new BPs could accelerate the physiological matrix turnover, they are more able to preserve the soft tissue surrounding bone as they have neither inflammatory effects nor toxicity, along with reduced effects on the cell viability, which are instead typical side effects of ZA administration. We can conclude that the newly synthesized compounds are better tolerated, leading to the hypothesis that their use leads to connective tissues side effects reduction compared to clinically used drugs, even though several studies are required to deeply investigate the signaling cascades involved in the mechanism of action of these new BPs.

References

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Keywords
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