BONE MINERALIZATION AND VASCULARIZATION IN BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW: A RAT MODEL

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INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a major adverse event due to bisphosphonates (BPs). It is clinically defined as an area of exposed bone of the jaws. The pathogenesis of BRONJ is not fully explained and seems multifactorial. An antiangiogenic effect of some BPs (e.g., zoledronic acid – ZA) on jaw bone vascularization has been advocated. The aims of the present study were to induce BRONJ in the rat, to analyze the alveolar mandibular vascularization and to assess the quality of the bone by evaluating the mineralization degree of the bone matrix.

MATERIALS & METHODS

38 adult male Sprague Dawley rats were randomized into 2 groups: CTRL (n=11) ZA (n=27)

Rats of the ZA group received a weekly intravenous injection of ZA (100 μg/kg) during 10 weeks.

Rats of the CTRL group received a similar injection of saline.

Right mandibular extraction of the 3 molars was performed in all rats of the study at the 6th week.

Euthanasia of rats was done 14 weeks after the first injection (CO₂ inhalation).

Microtomography (MicroCT) was used to study bone lesions. Vascularization analysis was performed after intravascular injection of a radio-opaque material and 3D analysis by microCT. Raman microspectroscopy was performed on the alveolar bone of the molar area to evaluate bone mineralization.

RESULTS

Bone exposure at extraction sites was found in 55% of the ZA treated rats and no bone exposure was found in other location and in rats of the CTRL group.

MicroCT analysis revealed numerous signs of BRONJ at the right molar area in the ZA group.

Vascular density of the molar area appeared significantly increased on the right side in the CTRL group due to tooth extraction. It was reduced in the right side of the ZA group.

Raman analysis showed significantly increased mineral to amide-I (band 960/1666cm⁻¹; p=0.031) and mineral to amide II (band 960/1545cm⁻¹; p=0.021) ratios in alveolar bone after impregnation with ZA.

CONCLUSION

In a rat model of BRONJ with mandibular tooth extraction, MicroCT evidenced signs of osteonecrosis. However, vascularization was not suppressed by ZA but reduced after tooth extraction. The anti-angiogenic effect of BPs may have a role in the pathophysiology of ONM. Raman spectroscopy evidenced an increased mineralization of the alveolar bone after prolonged treatment with ZA.