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Chronic alendronate therapy impairs epithelial morphology and homeostasis in the human oral mucosa

Elena Donetti[1], Alice Gualerzi[1], Giovanni Lodi[2], Davide Passera[2], Laura Cornaghi[1] and Andrea Sardella[2]

[1] Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milano, Italy
[2] Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi di Milano, Milano, Italy

Alendronate (ALN) is a nitrogen containing bisphosphonate (BP) widely used for the chronic treatment of osteoporotic patients, especially women over 60 years old. The diffusion of BPs in clinical practice has brought attention to one of their most serious side-effects, osteonecrosis of the jaw (ONJ) [1]. Several theories have been proposed to explain its pathogenesis, but the effect of BPs on the oral mucosa is still matter of debate despite its extensive involvement and injury in ONJ. This study aimed at evaluating from a morphological point of view the effects of ALN therapy on the oral epithelium of clinically healthy keratinized oral mucosa.

Six women over 60 years old undergoing chronic therapy (2-7 years) with oral ALN after diagnosis of osteoporosis were recruited and compared to a gender and age matched group (n=6). Smoking habit, past history of head and neck cancer treatment, and concomitant assumption of steroidal and antiangiogenic drugs were excluding criteria. Proliferation, apoptosis, intercellular adhesion, and terminal differentiation were investigated by immunofluorescence and transmission electron microscopy (TEM).

A significant decrease in keratinocyte proliferation was detected in the oral epithelium of patients undergoing ALN therapy compared to the control group (237.62 BrdU/mm2 ± 92.22 vs 104.16 BrdU/mm2 ± 66.20; $p = 0.0002$), without any sign of apoptosis induction by light microscopy and TEM. The presence of well established adherens and tight junctions was accompanied by profound alterations in desmosomal ultrastructure and molecular composition in the uppermost layers of the oral epithelium of the ALN group. Proceeding from the lower spinous to the granular layer, TEM analysis showed a progressive reduction in desmosomal thickness paralleled by a lower immunostaining for desmoglein 1 and desmoglein 3 in the suprabasal keratinocytes. In the upper epithelial layers, intermediate filaments gradually aggregated forming electron-dense bundles detached from the desmosomal plaque and a significant decrease in keratin 10 expression was observed. Taken together the reported results suggested a profound impairment in structure and function of the clinically healthy oral epithelium related to chronic ALN assumption. For the first time our results show that epithelial homeostasis in human oral mucosa is profoundly affected by nitrogen containing BPs, confirming previous in vitro studies [2-4] and strongly supporting the need of further investigation on the molecular mechanisms involved in ONJ pathogenesis.

References

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