Á. Janovszky¹, R. Varga¹, A. Szabó², D. Garab², M. Boros², J. Piffkó¹
¹Department of Oral and Maxillofacial Surgery, ²Institute of Surgical Research, University of Szeged, Hungary

Examination of the microcirculatory consequences of chronic zoledronic acid treatment in a rat model.

Introduction: The significance of bisphosphonate (BIS) therapeutic modality has been increased due to the elevated incidence of tumorous cases with bone metastasis and osteoporosis. Osteonecrosis of the jaw can occur as an adverse-effect, it mainly develops in third-generation bisphosphonate-treated patients after tooth extraction.

Objective: We hypothesized that inflammatory processes play a role in the development of BIS-related osteonecrosis. Our aim was to investigate the microcirculatory effects of BIS treatments in the periosteum of the jaw in a clinically relevant chronic animal model.

Material and Methods: 30 Sprague-Dawley rats were used; the animals were randomly allotted to one or another of the following groups: vehicle-treated control (n=10), intraperitoneal BIS treatment (n=10, IP) or intravenous BIS treatment (n=10, IV), respectively. BIS (zoledronic acid, Zometa, Novartis Europharm) was used in a dose of 80 µg/kg; ip. injections were given 3 times a week over 6 weeks, while iv. treatments were applied once a week over 8 weeks. In the third week of experiments, first molar extractions were performed at both sides of the mandible. Microcirculatory cellular reactions were examined by intravital microscopy in the periosteum of the mandible corpus and in the tibial periosteum. The NADPH oxidase activity of neutrophil leukocytes was measured by luminometry, the expression of adhesion molecule CD11b by flow cytometry, and plasma levels of tumor necrosis factor-α (TNF-α, ELISA technique) were assessed.

Results: Gingival wound healing disturbances occurred in 55% after both forms of chronic BIS treatments. The ip and iv BIS treatments did not affect the microvascular red blood cell velocity, but the number of rolling and adherent leukocytes was increased in the postcapillary venules of the mandible. The number of firmly adherent leukocytes was increased in the tibial periosteum as well. The expression of adhesion molecule CD11b or plasma levels of TNF-α were not affected by BIS treatments, however the NADPH oxidase activity of leukocytes was lower as compared to the control group.

Conclusion: Our data demonstrate that chronic BIS treatment is accompanied by characteristic mandibular periosteal microcirculatory inflammatory reactions. This suggests a potential role for leukocytes in the propagation of jaw osteonecrosis.

Grant support: TÁMOP-4.2.2/B-10/1-2010-0012 project: “Broadening the knowledge base and supporting the long term professional sustainability of the Research University Center of Excellence at the University of Szeged by ensuring the rising generation of excellent scientists.”