

LETTER TO EDITOR

Comments on ‘Bisphosphonate and statin: adverse effects of co-medication on wound healing in *in vitro* models of periodontal tissues’

David Szaraz^{a,b}, Vojtech Perina^{a,b} and Petra Borilova Linhartova^{a,c}

^aClinic of Maxillofacial Surgery, University Hospital Brno, Brno, Czechia; ^bFaculty of Medicine, Masaryk University, Brno, Czechia; ^cRECETOX, Faculty of Science, Masaryk University, Brno, Czechia

ABSTRACT

This is a comment on the article ‘Bisphosphonate and statin: adverse effects of co-medication on wound healing in *in vitro* models of periodontal tissues’ <https://doi.org/10.2340/aos.v85.45585>

ARTICLE HISTORY

Received 15 May 2026
Accepted 24 May 2026

KEYWORDS

Bisphosphonate;
alendronate; statin;
simvastatin; osteonecrosis

Dear Editor,

The recently published article titled ‘Bisphosphonate and statin: adverse effects of co-medication on wound healing in *in vitro* models of periodontal tissues’ from Småland-Reksten et al. [1] sparked great interest in our research team. Their research focused on the much-needed topic of the impact of concomitant influence of simvastatin (SIM) and alendronate (ALN) on wound healing. The study revealed that not only do these two drugs seem to have a synergistic adverse effect on bone turnover, but also SIM alone can in higher doses alter wound healing just as much as the combination of the two drugs.

Two years ago, we published a case report on a rare case of medication-related osteonecrosis of the jaw (MRONJ), which occurred just after a single low dose of denosumab (DMB) [2]. In that paper, we argued that previous atorvastatin and ALN medication predisposed the patient, yet DMB was the trigger of MRONJ development. Based on a review of four papers of MRONJ after statin medication in our article [3–6], we also proposed that statins probably have a pleiotropic effect in a dose-dependent manner. Based on that observation, we speculated that lower doses of statins and short-term medication support angiogenesis, while higher doses and long-term medication inhibit it. In a recent *in vivo* study using a mouse model, Bae et al. observed that an antibody against vascular endothelial growth factor (VEGF, one of the key factors in angiogenesis) delays the healing of osteomucosal wounds but does not cause bone necrosis on its own [7]. Rather, it is the combination of osteoclast suppression and angiogenesis inhibition that is considered a risk factor for the development of MRONJ [7].

It is interesting to see in the study by Småland-Reksten et al. that VEGF peaked after the first day of SIM exposure (whether

alone or combined with ALN). This may explain why some studies reported beneficial effect of statins on healing where statins were usually given in a single dose [8–10]. However, as this paper shows, the continuation of SIM actually causes a decrease in VEGF. We are happy to see that we found support to our hypothesis [2] in this recent paper, suggesting that duration might be just as important as dosage. In fact, Adachi et al. observed that experimental models of MRONJ in which higher doses of fluvastatin (but only in a single dose) were administered had a better overall outcome compared to those with lower doses [9]. However, besides the effect of statins on VEGF, it is noteworthy that statins and ALN both act through the mevalonate pathway [5], constituting a crucial signaling pathway in bone turnover. This may further explain the synergistic effect of statins and bisphosphonates.

It would be also interesting to investigate the possible interactions between SIM and DMB or SIM, bisphosphonates, and DMB on both soft and hard tissues in oral cavity. We would like to congratulate the research team for the great success achieved in their study. We hope to see more research published on this topic.

Acknowledgements

The authors thank the Research Infrastructure RECETOX RI (No LM2023069, MEYS CR, 2023–2026). This work was supported by a project of the University Hospital Brno, Ministry of Health of the Czech Republic – RVO (FNBr, 65269705, Sup 45/23) and Program JAC – Project SALVAGE, no. CZ.02.01.01/00/22_008/0004644 – co-funded by EU. This work was supported from the European Union’s Horizon 2020 research and innovation program under grant agreement No 857560 (CETOCOEN

Excellence). This publication reflects only the author's view, and the European Commission is not responsible for any use that may be made of the information it contains.

References

- [1] Småland-Reksten A, Agger AE, Lian AM, Reseland JE, Krüger TB. Bisphosphonate and statin: adverse effects of co-medication on wound healing in in vitro models of periodontal tissues. *Acta Odontol Scand.* 2026;85:125–33. <https://doi.org/10.2340/aos.v85.45585>
- [2] Száraz D, Peřina V, Treglerová J, Macháček C, Zendulka O, Bořilová Linhartová P. Case Report: single low-dose of denosumab as a trigger of MRONJ development in a patient with osteoporosis after bisphosphonate therapy. *Front Oral Health.* 2024;5:1473049. <https://doi.org/10.3389/froh.2024.1473049>
- [3] Aghaloo TL, Tetradis S. Osteonecrosis of the jaw in the absence of antiresorptive or antiangiogenic exposure: a series of 6 cases. *J Oral Maxillofac Surg.* 2017;75:129–42. <https://doi.org/10.1016/j.joms.2016.07.019>
- [4] Nordin J, Ghazali AB. Osteonecrosis of the jaw in patients taking Atorvastatin: case series. *IJOHS.* 2022;3:219–22. <https://doi.org/10.31436/ijohs.v3i2.73>
- [5] Giladi HZ, Gabay E, Machtei EE. Medication-related osteonecrosis of the jaw in patients taking high-dose simvastatin. *J Oral Maxillofac Surg.* 2020;78:862–3. <https://doi.org/10.1016/j.joms.2020.01.009>
- [6] Samieirad S, Labafchi A, Famili K, Hashemzadeh H. Medication-related osteonecrosis of the jaw (MRONJ) due to simvastatin: an unusual case report. *World J Plast Surg.* 2021;10:132–5. <https://doi.org/10.29252/wjps.10.1.132>
- [7] Bae E-B, Kim M-Y, Ji S, Cho I-W, Kim SY, Esmaili M, et al. Anti-VEGF neutralizing antibody delays osteomucosal healing by reducing collagen formation in mice. *Sci Rep.* 2025;15:36903. <https://doi.org/10.1038/s41598-025-20840-x>
- [8] Tan J, Yang N, Fu X, Cui Y, Guo Q, Ma T, et al. Single-dose local simvastatin injection improves implant fixation via increased angiogenesis and bone formation in an ovariectomized rat model. *Med Sci Monit.* 2015;21:1428–39. <https://doi.org/10.12659/MSM.892247>
- [9] Adachi N, Ayukawa Y, Yasunami N, Furuhashi A, Imai M, Sanda K, et al. Preventive effect of fluvastatin on the development of medication-related osteonecrosis of the jaw. *Sci Rep.* 2020;10:5620. <https://doi.org/10.1038/s41598-020-61724-6>
- [10] Yasunami N, Ayukawa Y, Furuhashi A, Atsuta I, Rakhmatia YD, Moriyama Y, et al. Acceleration of hard and soft tissue healing in the oral cavity by a single transmucosal injection of fluvastatin-impregnated poly (lactic-co-glycolic acid) microspheres. An in vitro and rodent in vivo study. *Biomed Mater.* 2015;11:015001. <https://doi.org/10.1088/1748-6041/11/1/015001>