Bisphosphonates that lack a nitrogen-containing side chain do not cause osteonecrosis of the jaws, regardless of their effect on STAT3 phosphorylation and SOCS3 expression

In reply:

We provide the following response to the author's statement that because both the non-nitrogen and nitrogen-containing bisphosphonates inhibit SOCS3, it must be largely irrelevant in the understanding of bisphosphonate-associated/bisphosphonate-related osteonecrosis of the jaw (BAONJ/BRONJ) because this syndrome only occurs with patients treated with nitrogen-bisphosphonates (N-BPs). Given that ONJ occurs within patient populations that have been administered high doses of these compounds, we agree with the author that, along with their accumulation in bone, the increased potency observed with the N-BPs factors into their therapeutic effects and may play a role in their adverse effects as well. BPs have been implicated in BAONJ/BRONJ development, and at least 1 publication has demonstrated an ONJ-like disease in a mouse model after combined zoledronic and glucocorticoid treatment.[1] Also of note is the intriguing discovery in this model that the number of osteoclasts increased with long-term bisphosphonate use.

Yet, BPs are not required for ONJ to occur. Evidence for the incidence of BAONJ/BRONJ with the use of the anti-RANKL antibody denosumab (trade names: XGEVA, Prolia),[2,3] as well as the antineoplastic agent sunitinib (Sutent),[4-6] a receptor tyrosine kinase inhibitor, has been reported in their Food and Drug Administration–approved drug labels. The dissimilar mechanisms of action for these agents indicate that inhibition of farnesyl pyrophosphate synthase is not necessary for the development of BAONJ/BRONJ unless this inhibition occurs as an additional unreported effect.

To date, we do not have sufficient data to propose decreased suppressor of cytokine signaling 3 (SOCS3) levels as a mechanism for the development for BAONJ/BRONJ. However, decreased levels of SOCS3 have been correlated with an incidence of ONJ (unpublished data, personal communication, E. Scheller, University of Michigan). This is not surprising, as SOCS3 is a major player in the regulation of inflammatory cytokine signaling.[7-11] The purpose of our publication is to illuminate a novel relationship between bisphosphonate use and a protein that sits at the crossroads of inflammatory responses and osteoclast development.[12]

Nevertheless, it cannot be ignored that SOCS3 appears to play a role in osteoclastogenesis.[13-15] Review of the current literature reveals a number of propsed models attributing BAONJ/BRONJ to infection and subsequent release of significant amounts of N-BPs resulting in an inability to resolve the resulting inflammation and promote healing.[16-19] Therefore, targeting SOCS3 could provide a means to regulate inflammation before osteonecrotic events, but additional studies are necessary to clarify its specific role. If anything, our study provides further credence to the putative role of inflammation in the development of BAONJ/BRONJ.

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Two-stage split-crest technique with ultrasonic bone surgery for controlled ridge expansion: a novel modified technique

To the Editor:

In patients with long-standing edentulous arches, extreme bone resorptions (both vertically and horizontally or combined defects) are frequently observed. Bone augmentation procedures represent an effective treatment option when there is a lack of supporting bone as a result of atrophy, trauma, or surgical resection. The "split-crest" technique consists of splitting the vestibular and buccal cortical tables[1,2] and displacing the vestibular cortical bone in maxilla or mandible to create a middle gap, which is usually occupied mostly by the inserted implants. The unoccupied space by the implants can be filled with biomaterials, such us autologous bone grafts, particulate bone, or autologous biological therapies, such as plasma rich in growth factors (PRGF-Endoret).[3-6] However, the use and predictability of the conventional split-crest technique is limited when the alveolar ridge is reabsorbed into the apical or occlusal points.

This study reports the clinical evaluation of a novel technique based on a modification of the conventional split-crest expansion technique. This procedure is indicated in cases of extremely resorbed ridges (3-4 mm) and consists of expanding the bone in 2 consecutive stages using transitional implants. The approach presented herein provides a twofold or even threefold increase in the width of the ridge, facilitating the placement of large-diameter implants that otherwise could not be inserted with the conventional 1-stage technique. The status of the soft and hard tissues surrounding the implants, and the success of inserted implants have been carefully analyzed.

Between March and September 2008, 3 patients received 4 implants (BTI Biotechnology Institute, Vitoria, Spain) after a 2-stage split-crest technique performed with ultrasonic bone surgery and using transitional narrow-diameter implants. The clinical histories of all patients were carefully evaluated to obtain the necessary demographic and anthropometric data, and clinical backgrounds of patients.

The procedure was performed in 2 stages. The first stage consisted a conventional split-crest procedure involving the opening of a full-thickness flap, after which scaling with the ultrasonic spoon around the bone bed was performed with the aim of stimulating bone bleeding. The starting drill was used to localize the sites where transitional implants were placed. Using an ultrasonic flat chisel, a side-to-side cut in the osseous crest was performed to connect the holes previously created (Fig. 1, *a* and *b*). At that point, the expansion was begun using the different motorized expanders (BTI Biotechnology Institute). The expansion was performed by means of the necessary drills (BTI Biotechnology Institute) depending on bone width and the type of implant to be placed (Fig. 1, *c*). The drilling sequence was 1.8-, 1.8- to 2.5-, 2.5-, and exceptionally 3.0-mm drills. Then, implants were placed (Fig. 1, *d*) and the "gap" on the ridge was overcorrected using an initial graft made of autologous bone mixed with liquid PRGF-Endoret (BTI Biotechnology Institute), a second layer consisting of porous bovine inorganic freeze-dried bone (BIOSS, Geistlich, Switzerland) mixed with liquid PRGF, and a final layer of fibrin membrane obtained from PRGF technology. Closure was made without tension. Once the osseointegration period was completed (4-6 months), a new full-thickness flap was performed to access to the previously inserted implants, which were covered by the gum (Fig. 1, *e* and *f*). The implants that had to be replaced by larger diameter ones were retrieved using the BTI Extraction Kit (BTI Biotechnology Institute) (Fig. 1, *g*). Once the transitional implant was atraumatically removed, a new drilling sequence was performed to place the definitive implants. The latter favored a new expansion process, compacting the native bone and enhancing the horizontal bone ridge width (Fig. 1, *h*). The ridge was overcorrected if necessary, following the same protocol described previously. Implants were loaded in function 4 to 6 months later.