Tohoku J. Exp. Med., 2019, **248**, 27-29

Commentary

Antiresorptive Agents and Anti-Angiogenesis Drugs in the Development of Osteonecrosis of the Jaw

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Medication-related osteonecrosis of the jaw (MRONJ) is a condition of exposed bone in the maxillofacial region, which occurs among subjects treated with antiresorptive agents or anti-angiogenesis drugs, despite the lack of a history of head or neck radiation treatment. Although there are still many points to be clarified about the mechanism of MRONJ, it is possible to hypothesize a common pathogenetic mechanism for two different classes of drugs: antiresorptive and anti-angiogenetic drugs. These drugs can inhibit angiogenesis by interfering with endothelial cell proliferation and survival, leading to loss of blood vessels and avascular necrosis. This hypothesis could be of immediate translational interest. Targeting the anti-angiogenetic effect of the antiresorptive agents could provide a new possibility for the prevention of treatment of MRONJ.

Keywords: anti-angiogenesis agents; antiresorptive agent; bisphosphonates; denosumab; medications-related osteonecrosis of the jaw
Tohoku J. Exp. Med., 2019 May, **248** (1), 27-29.

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Medication-related osteonecrosis of the jaw (MRONJ) is a condition of exposed bone in the maxillofacial region, which occurs among subjects treated with antiresorptive agents or anti-angiogenesis drugs, despite the lack of a history of head or neck radiation treatment. In the recent article, "Antiresorptive Agent-Related Osteonecrosis of the Jaw (ARONJ): A Twist of Fate in the Bone" (Shibahara 2019), the Author outlines the notion of MRONJ by examining antiresorptive drugs and the status of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in Japan.

In his valuable work, the Author reports correctly that in 2014 the American Association of Oral and Maxillofacial Surgeons proposed the term "MRONJ" to indicate osteonecrosis of the jaw (ONJ) provoked by antiresorptive agents as well as anti-angiogenesis drugs (Ruggiero et al. 2014). The anti-angiogenesis substances include human monoclonal antibodies, anti-vascular endothelial growth factor (VEGF), tyrosine kinase inhibitors, thalidomide, and mTOR inhibitors (Nicolatou-Galitis et al. 2019).

The possibility that two different categories of drugs can determine the same alterations deserves a close examination. In fact, there are still many points to be clarified about the mechanism of MRONJ. Based on the literature, however, it is possible to hypothesize a common pathogenetic mechanism for the two different classes of drugs. The disease probably has a multifactorial genesis (infections, accumulation of necrotic bone, etc.), it is in any case avascular necrosis (Fig. 1).

It is well known that bisphosphonates (BPs) decrease endothelial proliferation in cultured human umbilical vein and rat aortic ring cells (Wood et al. 2002), and in previous studies we have shown the possibility that BPs can influence the phenomena of angiogenesis (Allegra et al. 2007, 2010). In fact, BRONJ patients showed a decrease of circulating endothelial progenitor cells (CEPCs) compared to controls (Allegra et al. 2007). Moreover, we found an increase in endothelial cell apoptosis after BPs administration among patients with multiple myeloma and ONJ subjects (Allegra et al. 2010). These findings are in agreement with the hypothesis that BPs can block angiogenesis by interfering with endothelial cell proliferation and survival, leading to loss of blood vessels and avascular necrosis. This action could be due to the ability of BPs to reduce VEGF production, although we were not able to find a modification of the levels of soluble VEGF receptor 1 (Alonci et al. 2007). Using new molecules that inhibit VEGF such as pegaptanib, ranibizumab and bevacizumab, it was possible to see a similar action, with an increase in endothelial cell apoptosis (Carneiro et al. 2009). Analogously, employing a siRNA-targeting VEGF gene, it was possible to block the expression of VEGF at the mRNA level, and this provoked a reduction of the Bcl-2/bax ratio,

Received March 18, 2019; revised and accepted April 22, 2019. Published online May 11, 2019; doi: 10.1620/tjem.248.27.
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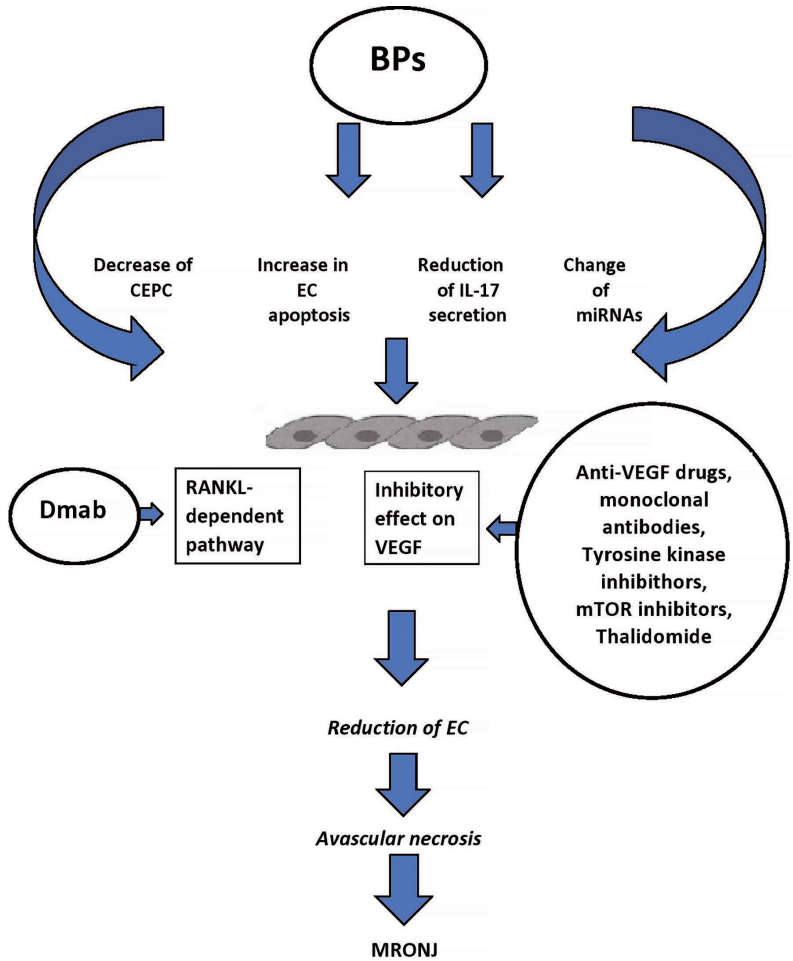

Fig. 1. Possible mechanisms in the onset of MRONJ.
The cell layer indicates vascular endothelial cells.
EC, Endothelial cells; CEPC, Circulating endothelial progenitor cells; BPs, bisphosphonates; Dmab, Denosumab.

and an increased expression of cleaved caspase 3 (Ge et al. 2009).

We measured serum concentrations of interleukin17 (IL-17), a member of a cytokine family, produced primarily by T cells, in patients with multiple myeloma treated with BPs (Oteri et al. 2008). IL-17 is a mediator of angiogenesis that stimulates vascular endothelial cell migration and regulates the production of a variety of proangiogenic factors such as VEGF and TNF alpha. BPs administration caused a significant decrease of circulating IL-17 serum levels (Oteri et al. 2008).

Finally, in a recent study, employing reverse transcription quantitative polymerase chain reaction, we evaluated miRNAs in peripheral lymphocytes of multiple myeloma subjects with BRONJ (Musolino et al. 2018). Our data revealed the existence of a diverse miRNA signature for ONJ patients with respect to control subjects. We recognized 14 dysregulated miRNAs. All these miRNAs were significantly over-expressed in BRONJ, and they targeted several pathways and genes. Two of the examined miRNAs (23A and 520E), can control cell cycle and angiogenesis and so they could have a central action in BRONJ (Musolino et al. 2018). Although our work has been carried out on a small number of patients, we are trying to confirm the results obtained on a larger series and attempting to evaluate the possible existence of a different pattern also for the long non-coding RNA.

Finally, Denosumab (Dmab) is a fully human monoclonal antibody with high affinity for RANKL and has a diverse mechanism of action from BPs. However, the Dmab medication is also associated with ONJ (Egloff-Juras et al. 2018), and the incidence of onset of MRONJ is equal to that of BPs.

Dmab has no soft tissue toxicity, unlike BPs, and in theory, Dmab-related ONJ disease could have appearances unlike that of BRONJ. Reduction of bone turnover due to a decrease of osteoclastogenesis by Dmab is almost certainly the main reason for the onset of the Dmab-related ONJ (Khan et al. 2015). Yet, Girolami et al. (2016) reported an antiangiogenic activity of denosumab in giant cell tumor of bone, probably mediated by a RANKL-dependent pathway.

It must be considered that the various mechanisms underlying the pathology can be strengthened between them. ONJ is a disease befalling only in the jaw bones,

which have specific microbiological features that dispose them to bacterial infections. The oral mucosa protecting the jawbone is thin, and thus infection provoked by mucosal damage can reached the bone. Moreover, more than 800 varieties of bacteria inhabit oral mucosa (Allegra et al. 2019) and bacteria also cause bone resorption through the generation of local cytokines and participate to bone necrosis. For instance, BPs exhibit direct necrotic effects on soft tissues, and these actions are increased by lipopolysaccharide, a bacterial-cell-wall component.

All these data could be of immediate translational interest. Targeting the antiangiogenetic effect of the antiresorptive agents could provide a new possibility for the prevention or treatment of MRONJ.

Conflict of Interest

The authors declare no conflict of interest.

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