Editorial

Platelet Growth Factor-enriched Plasma Therapy for Bisphosphonate-related Osteonecrosis of the Jaw: Biological Basis and Case Studies reviewed

Bisphosphonates (BPs) are widely used in the management of numerous bone pathologies, such as osteoporosis, Paget's disease, malignancy-induced hypercalcemia, bone loss accompanying multiple myeloma and inflammatory conditions.[1-6] Although bisphosphonates, such as alendronate, pamidronate and zoledronic acid are effective in the management of fractures and bone pain, there are associations of the long-term use of these drugs with atypical fractures of the femur and osteonecrosis of the jaw.[7,8] Since the first report by Marx in 2003 on the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ), there is wide-spread recognition of this complication as a pathology that dental clinicians can expect to find in some of their patients taking BPs.[9]

Bisphosphonate-related osteonecrosis of the jaw is defined as an avascular area of necrotic bone in the maxillofacial region that has been present for more than 8 weeks, and that may or may not have associated exposed bone. It occurs in patients who have received and/or are receiving BPs without previous irradiation in the maxillofacial region.[10] Bisphosphonate-related osteonecrosis of the jaw is particularly prevalent in patients who receive intravenous administration of BPs and are often cancer patients. The lesion associated with BRONJ can progress if not managed and can lead to painful complications including altered sensations in areas, such as the inferior alveolar nerve, oroantrol or oronasal communication, fistulae of intraoral or extraoral nature as well as mandibular fractures.[10] At present, management of BRONJ is controversial with treatment involving topical and surgical approaches.[11]

An effective treatment of BRONJ using growth factors from the patient's own plasma has been developed by clinicians based on results of basic bone biological studies and case studies of individuals suffering from the painful complications.

There are a number of reports on the therapeutic effects of platelet-derived growth factor (PDGF) on the regeneration of alveolar bone, periodontal tissues as well as wound healing in general.[12-16] Local applications of PDGF-BB have been shown to destabilize blood vessels and result in growth of new vasculature at the site of the healing wound.[17] In our laboratory, we have shown that the stimulatory effects of PDGF on growth and differentiation of human alveolar osteoblastic cells were maintained when cells were coincubated with alendronate, a widely used BP, suggesting that the growth factor might be useful therapeutically to minimize potential negative effects of BPs.[18] This is in agreement with data from another one of our studies showing that osteoblastic cells isolated from patients with BRONJ responded to PDGF in a positive manner similar to cells isolated from alveolar bone of persons not treated with BPs.[19]

Studies have reported that pamidronate and zoledronic acid, given to cancer patients before chemotherapy, can produce significant decreases in PDGF as well as angiogenic factors, such as vascular endothelial growth factor (VEGF).[20,21] Decreases of this nature in the concentrations of factors that have significant effects on osteoblastic and osteoclastic cells can influence the overall effects of the BPs on bone remodeling and lead to an osteonecrotic condition. These studies are consistent with the notion that growth factors, such as PDGF, could be a natural therapy for BRONJ.

There is a growing body of literature that suggests that a patient's own plasma can be used as a source of growth factors by relatively simple centrifugation techniques to form platelet growth factor enriched plasma (PRGF). Local application of this plasma that has levels of PDGF and other growth factors, such as VEGF, concentrated at relatively high levels, can have beneficial therapeutic effects in the healing aspect of a number of different clinical conditions that appear to be also applicable to BRONJ.[22]

A report by Adornato et al[23] documented that after a period of 6 months, 10 out of 12 patients with refractory BRONJ who were treated with a combination of bone resection and autologous platelet-derived growth factors, had complete recovery of mucosal and bony defects and the other two manifested some improvement in healing. Subsequently, Mozzati et al[24] reported successful treatment of 32 cases of BRONJ with local application of PRGF

after resection of the necrotic tissue. A 7-year follow-up by this group documented 100% recovery from BRONJ in these patients.[25] Most recently, another report of 72 successful cases of treatment of BRONJ with PRGF can be found in the clinically descriptive review of Longo et al.[26] Although the number of such cases reported in the literature has rapidly increased, case-control randomized studies to support the use of PRGF therapy for BRONJ are still lacking.[26]

Considering the complexities of the presentation of the osteonecrotic lesions and the spectrum of underlying conditions in the patients who present with BRONJ, control studies might be difficult to achieve. In the meantime, careful observation of patients who have had BPs therapy is warranted to avoid development of osteonecrotic lesions. In patients who do develop BRONJ, PRGF therapy should be considered as a component of the treatment plan based on sound scientific studies on the biological effects of growth factors on bone cells and a growing number of published case reports on its successful outcomes.

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