

New Alternatives on the Treatment of Bisphosphonates Related Osteonecrosis of the Jaws: A Review and Case Study

Revisión de Literatura sobre Nuevas Alternativas en el Tratamiento de la Osteonecrosis Maxilar por Bisfosfonatos: Estudio de un Caso

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Abstract

Bisphosphonates are drugs that are used to prevent bone resorption and as an antitumor therapy in the control of metastasis. Nevertheless, they are not exempt from adverse effects, the most frequent of these being osteonecrosis of the jaws (ONJ). Due to a clinical case, a literature revision is performed with the aim of getting to know the new therapeutic procedures that are available for the treatment of ONJ. Different alternative therapeutic methods are currently being used for its treatment. These range from the use of laser, hyperbaric oxygen therapy, ozone therapy, the administration of teriparatide, stem cells immunotherapy and the use of L-PRF membranes. The modern inclusion of these new therapies in the treatment of ONJ, has contributed to the creation of numerous studies which aim to test the efficacy of these new procedures, achieving hopeful results.

Palabras clave: jaws, osteonecrosis, bisphosphonates, treatment.

Resumen

Los bisfosfonatos son fármacos empleados para evitar la reabsorción ósea y como terapia antitumoral en el control de la metástasis. No obstante, no son compuestos exentos de producir efectos adversos, siendo el más frecuente la osteonecrosis de los maxilares (ONM). A propósito de un caso clínico, se realiza una revisión de la literatura con el objetivo de conocer los nuevos procedimientos terapéuticos disponibles para el tratamiento de la ONM, entre las que encontramos la utilización del láser, la terapia con oxígeno hiperbárico, la ozonoterapia, la administración de teriparatida, la inmunoterapia con células madre y el empleo de membranas de L-PRF. La inclusión en el tratamiento de la ONM de estas nuevas terapias ha propiciado la elaboración de numerosos estudios con el objetivo de comprobar la eficacia de estos nuevos procedimientos, obteniendo resultados esperanzadores.

Keywords: osteonecrosis maxilar, bisfosfonatos, tratamiento.

Introducción

Bisphosphonates (BPs) modulate bone metabolism and they are utilized in the treatment of diseases that deal with bone resorption, such as Paget disease, osteoporosis or hypercalcemia related to different malignancies like multiple myeloma or bone metastasis. BPs inhibit bone resorption limiting osteoclastic activity, although it is also considered that they have an antiangiogenic effect, therefore, they are also used as antitumor therapy. However, the use of BPs and other antiresorptive drugs can cause adverse effects, the most serious and studied of which is osteonecrosis of the jaws (ONJ).

ONJ is defined as an area of necrotic bone which does not heal under 8 weeks in patients who have been treated with BPs without a history of radiotherapy in the maxillary region. The prevalence of ONJ is much higher in patients treated with intravenous BFs (0-0.348%) in comparison with oral BFs (0.001-0.10%). Systemic risk factors of ONJ depend on the route of administration, the accumulated dose, the length of the treatment, the disease for which BP has been prescribed, gender or age, Local risk factors include dentoalveolar surgeries, mainly extractions, infections and the use of removable prosthesis. The diagnosis is fundamentally clinic. We need to take into account that there may be various locations of bone exposure and that these may remain entirely asymptomatic for a long period of time. On the other hand, we can detect signs and symptoms that are compatible with the pathology, such as pain or mucous ulceration, before ON is clinically detectable. Radiographic signs range from a variable radiopacity or radio-transparency to a total absence of radiographic signs, for this reason, many of the authors coincide in that radiographic signs are not precise to detect ONJ.

The aim of this project is to describe, a purpose of a clinical case, the new therapeutic alternatives that we currently have for the treatment of osteonecrosis associated with bisphosphonates, which range from hyperbaric therapy, ozone therapy, the use of laser, the administration of teriparatide, immunotherapy through stem cells and the use of fibrin membranes rich in platelets and leucocytes.

Clinical case

The clinical case of an 82-year-old male is presented, who goes to the clinic referred by his own dentist for extensive necrotic lesions in the maxillary, which do not produce any symptoms in the patient. He reports having noticed them two months ago. His clinical history reflects that it concerns a patient who is being treated for prostatic cancer from 11 years now, and due to his hip and bone metastasis, he is on medication with zoledronic acid (Zometa[®]) monthly, **goserelina** (Zoladex[®]) quarterly and prednisone. Additionally, he is in treatment with paracetamol, natecal, escitalopram, pantoprazole, acetyl salicylic acid and enalapril to control other pathologies. In his intraoral examination it is observed that the superior removable prosthesis is inappropriately adapted. When it is removed, multiple ulcerative lesions with exposed bone can be seen (Figure 1).

A diagnosis of osteonecrosis due to bisphosphonates is performed. It is also associated with other risk factors like the use of a badly adjusted removable prosthesis and probably to the use of prednisone and Zoladex which may delay the healing of tissues. However, the patient does not present any pain or perilesional inflammation. The treatment was as follows: Not to use a superior removable prosthesis, to use chlorhexidine 0.12% mouthwash (twice a day) to prevent overinfection, to perform a dental prophylaxis to remove plaque around the remaining teeth and to inform his oncologist and maxillofacial surgeon to evaluate possible measures.

Discussion

When ON occurs, the usual approach is an expectant conduct and in case of symptomatology, treatment for the infection and palliative treatment for the pain.

Surgical treatment. The surgical approach of this pathology is supported by several authors as they report high cure rates (59-90%) and improvement in stages, moreover, it is



Figure 1. Intraoral image of superior arch where multiple ulcerative lesions with bone exposure can be observed.

the only remedial treatment for refractory ON. Most authors are in favor of radical surgery, with segmentary resection of the jaw and partial maxillectomies, with the intention of achieving vital bone margins. (Holzinger et al., 2013)

Laser therapy. Low-powered lasers, thanks to their action modulating cellular metabolism, improving the healing of wounds, reducing pain, are very effective in the treatment of BPs related ON, especially in a treatment in conjunction with drugs. (Weber, Camilotti y Ponte, 2016)

Hyperbaric oxygen therapy (HBO). Daily treatment with HBO accelerates osteoblast differentiation rate, thus increasing the first stages of mineralization. This bases the use of HBO as an adjuvant treatment to prevent bone loss in those bone disorders that are associated with hypoxia, such as BPs related ON. In addition, HBO administration is capable of stimulating angiogenesis and they have a restorative action in case of bone loss due to osteonecrosis. (Al Hadi, Smerdon y Fox, 2015)

Ozone therapy. Ozone can improve the benefits in surgical and drug treatments of ON, when it is administered before and after dental treatments, in those patients who suffer from multiple myeloma and are in treatment with BPs. (Ripamonti, Cislighi, Mariani y Maniezzo, 2011)

Immunotherapy with stem cells (SC). Several cytokines released by SC have the action of activating cell angiogenesis and osteogenesis, thus, promoting the differentiation of osteoclasts and transcription factors for angiogenesis even in the presence of RANK-Ligand. Current studies get us closer to new therapeutics based on SC, which could be effective both in the treatment of ON and in reducing its occurrence, although more studies are necessary to conclude its efficacy. (Matsura et al., 20116)

Administration of teriparatide. Teriparatide is an analogue of the parathyroid human hormone formed by amino acids 1-34. It acts by stimulating osteoblasts, and promoting its differentiation and inhibiting its apoptosis, moreover, it significantly increases bone replacement, the volume, and bone density, improving the microarchitecture of both the trabecular and the cortical bone. Different studies have revealed that teriparatide could be an effective treatment in the prevention of ON, having as a result, an increased mineral bone density of the new bone formed in the cavity of the extraction, a reduced osteonecrotic area, in case there is necrosis, an increased number of osteoclasts and a lesser degree of inflammation in the healing stage. (Keskinruzgar et al., 2016)

The use of L-PRF (Leucocyte-rich and platelet-rich fibrin membranes). L-PRF is a leucocyte and platelet concentrate that is capable of realizing growth factors and proteins associated with the healing of wounds for more than 7 days *in vivo*, promoting cell proliferation and differenti-

ation, stimulating bone and soft tissue remodeling. The use of L-RPF in patients with bisphosphonates related osteonecrosis seems hopeful especially when the therapy is done in conjunction with BMP-2, although more studies are necessary to determine its true efficacy. (Kim, Kim y Kim, 2014).

Conclusion

Due to all this, it can be concluded that, although there is currently no agreement on the therapeutic focus of ONJ, in patients who present symptomatology, some barely invasive, effective techniques are being used to offer a good quality of life, as opposed to the surgical manipulation of the lesions. In early stages, which present no symptomatology a more conservative treatment is preferred.

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