Maxillary osteonecrosis: new evidence regarding its etiopathogeny

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Maxillary osteonecrosis (MON) is a disease which has appeared recently as a serious complication in patients suffering from neoplasms or other chronic diseases. MON has been associated with the use of powerful diphosphonates, for which reason many authors have named the disease secondary osteonecrosis of the mandible due to biphosphonates[1-5].

This is a relatively new disease, which means that there is not yet unanimity on many of its aspects. For a start, there is no clear and universally accepted definition of MON. A panel of experts from the American Society of Bone and Mineral Research (ASBMR)[2] recently recommended using the definition "an area of exposed bone which persists for more than 8 weeks in the absence of earlier irradiation and/or metastasis in the mandible". The American Academy of Mouth and Maxillofacial Surgeons published a similar definition: a patient may have MON if they comply with 3 requirements: 1) current or previous use of biphosphonates; 2) the presence exposed or necrotic bone for a minimum of 8 weeks; and 3) an absence of maxillary radiotherapy. At this point should insist that the correct name for the disease is maxillary necrosis and not necrosis of the mandible, given that there is frequently also affectation of the upper maxilla[6].

It used to be thought generally that MON was directly related to the use of biphosphonates, above all with those that are most powerful and administered intravenously, such as zoledronic acid or pamidronate. Thus, prestigious authors such as Reid have described MON as "a complication in the use of high doses of biphosphonates, which is characterised by the appearance of exposed bone in the oral cavity"[7].

The pathogeny of MON is unknown up until now, for which reason various theories relating to this have been developed[1,6,8,9]. Given that it has not been possible to identify one single cause, many authors have implicated various etiopathogenic factors, some of which may act in conjunction. In one way or another, the biphosphonates have always been present in these etiopathogenic theories. For example, one of these is based on the bone toxicity of biphosphonates, according to which the drug would accumulate in the bone in sufficient quantities to be directly toxic to the oral epithelium[1]. This would result in inadequate healing of lesions in the soft tissues, such as those observed in invasive dental procedures or by traumas produced by poorly-fitted prostheses, which could result in a secondary infection in the underlying bone[10]. However, against this theory, we have the fact that only the maxillas are affected, and not other bones where biphosphonates act equally. Another slightly different theory is that the biphosphonates accumulate in the alveolar bone, both in the upper maxilla and in the mandible, producing toxicity in the region of the soft tissues instead of in the bone[7].

However, against the theory that biphosphonates are the cause of MON we have, firstly, the fact that up to 25% of cases of MON have been described in patients who had not received this drug[6,8,10-14]. Secondly, many other risk factors have been described for this disease, such as diabetes *mellitus*, taking

corticoids, immunosuppressive treatment and rheumatoid arthritis, to name but a few[6,11,15,16]. These etiopathogenic factors are not mutually exclusive. In fact it is possible that MON could be a disease with a multifactorial etiopathogeny. On the other hand, it should also be taken into account that in up to 70% of cases there has been a dental intervention, such as teeth extraction, implants, etc.[3-6,8,10,14,16].

Finally, MON has been described in patients receiving denosumab, a monoclonal antibody against the protein RANKL, in 2 studies carried out in patients affected by cancer and who were randomly chosen to receive this drug, or zoledronic acid. In the first report, the prevalence of MON was 1.1% in those patients receiving denosumab and 1.3% in those who received zoledronic acid[17]. In another study, the prevalence of MON was 2% in those receiving denosumab and 1.4% in those who received zoledronic acid[18].

In conclusion, the new descriptions of MON in patients receiving denosumab ought to drive us towards re-examining the etiopathology of MON. Perhaps this disease is caused by an excessive repression of bone remodelling in patients with neoplasms, in whom the dose of these antiresorptive drugs used greatly exceeds that recommended for osteoporosis.

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