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Review Article

Osteonecrosis of the Jaw: Not All Bisphosphonates are the Same

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Abstract

Bisphosphonates (BPs) are drugs known since long time which now occupy a prominent position among therapeutic options for the prevention and treatment of various forms of bone diseases characterized by increased bone turnover. Although all have a similar bone tropism they have marked difference in the potency, mechanism of action and clinical tolerability. The overall clinical experience demonstrates that all BPs are very well tolerated when dosed and administered appropriately. Once absorbed, BPs bind to the bone mineral phase and are retained buried in the bone for extended period of time which vary from weeks, months up to years depending of the chemical structure of the various BPs. Despite good clinical tolerability, the widespread use of these drugs has also shown an increasing incidence of cases of osteonecrosis of the jaw (ONJ). ONJ is a severe pathology affecting the jaw bones of some patients treated for a long time with BPs. However, not all BPs have the same degree of risk, which is related to the different chemical structure, mechanism of action, and affinity for bone hydroxyapatite.

Keywords: *Bisphosphonates; BRONJ; Bone Turnover; Necrosis; Osteomyelitis*

Introduction

Since some decades the scientific community is having a large number of discussions and questions regarding some side effects related the use of bisphosphonates for treatment of bone diseases.

Bisphosphonates (BPs) are a category of drugs widely used for patients suffering from pathologies linked to alterations of bone metabolism. Although BPs have been employed in clinical practice for many years and have demonstrated an excellent safety profile [1], severe ONJ has recently been described in patients with bone metastases who were treated with BPs with cases becoming more frequent as the intravenous use of some BPs has become widespread in oncologic practice [2]. This has raised same questions: why might BPs, otherwise so well tolerated and even used to treat some cases of osteonecrosis of the femur and other bone areas, induce ONJ? Furthermore, why do we see only osteonecrosis in the jaw and not other areas? Questions that still now remain to be answered.

Brief story

However, although these doubts have arisen quite recently, the history of BPs dates back a long way, since sodium etidronate (Etidron-Didronel) was approved in Italy (1978) and in USA for the treatment of Paget disease of bone. This drug was followed a few years later (1985) by clodronate with an initial therapeutic indication aimed at subjects suffering from tumor osteolysis. If etidronate remained aimed at a limited number of patients, clodronate instead had wide application not only in Italy but also in other European and non-European countries including Japan. It must be remembered that while etidronate showed some side effects due to a possible inhibition of the degree of mineralization, clodronate was always very effective and well tolerated even after intravenous administration. These first BPs, defined as "first generation" were followed (1997) by other BPs with a different chemical structure and containing an amino group in the structure which led to definition of this group of drugs as Amino-derivatives (N-BPs). This category of drugs includes, in order of appearance on the market, Alendronate, for the treatment of osteoporosis, neridronate for osteogenesis imperfecta, followed by various other N-BPs presenting some structural variants (Risedronate-Ibandronate-Zoledronate) but with therapeutic indications aimed at both osteoporosis and tumor osteolysis (Zoledronate).

Although there has been widespread use of these drugs, for some years no side effects were reported that represented a serious risk for patients either in the treatment of OP or in patients with bone metastases despite high doses via the venous route. However, when the use of these drugs became extremely widespread, and in all countries, effects worthy of consideration began to appear and among these, in particular, the appearance of cases of jaw osteonecrosis in subjects under therapy with BPs and subjected to dental treatments or related to dental pathologies. A causal link has been finally established between osteonecrosis of the jaw and bisphosphonates intake and the condition was then named bisphosphonate-related osteonecrosis of the jaw (BRONJ).

There has been much discussion about this disease, which affects both mandibular and maxillary bones and not other areas of the skeleton, since cases of ONJ were presented in the scientific literature in a work by Marx RE in 2003 [2].

Bisphosphonates and ONJ

Since Marx reported on osteonecrosis of the jaw (ONJ) caused by the injectable amino bisphosphonates (N-BPs) pamidronate and zoledronate, there have been numerous reports in many countries of bisphosphonate-related osteonecrosis of the jaw (BRONJ) as a pathology similar to radiation-related osteonecrosis/osteomyelitis of the jaw, which is accompanied by exposure of the bone. Data that have appeared in the scientific literature regarding incidence of ONJ cases has led to a clear distinction between nitrogen-containing bisphosphonates (N-BPs) and non-nitrogen-containing BPs (non-N-BPs) [3] with case incidence of N-BPs definitely at higher risk of ONJ than non-N-BPs and in particular than Clodronate. Some studies on the incidence of ONJ, and data derived from various associations, report how the incidence of BRONI due to oral BPs is estimated to be 0.01% of patients according to AAOMS [4]; 0.01 - 0.04% by the European Association for Cranio-Maxillo-Facial Surgery (EACMFS) [5] and 0.001 - 0.069% by the International Task Force on Osteonecrosis of the Jaw [6]. In Japan, the incidence of BRONJ due to oral BPs was estimated to be 0.01 - 0.02% [7]. However, BRONJ due to high dose BPs was estimated to be 0.8-12% by the AAOMS (Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons 2007), 0.88 - 1.15% by the EACMFS and 1 - 2% in Japan.

ONJ is a rare but serious complication that can arise, after some dental procedure, in patients who took or is taking antiresorptive agents, leading to visible bone or a fistula whose risk has been linked to a chronic use of BPs as well as to the use of a different inhibitor of osteoclasts activity like denosumab. Denosumab is a monoclonal antibody which binds to and inhibits the receptor activator of NF-κB ligand (RANKL). In bone, RANKL is produced by several cell types, including osteoblasts, osteocytes, stromal bone cells and immune cells and is a major regulator of osteoclast precursor commitment and osteoclast differentiation and function. Through the RANKL binding action, denosumab inhibits osteoclastic numbers and activity [8].

Although BRONJ was initially investigated since 2003, the pathophysiology of the disease remains largely unknown. Multiple hypotheses have been proposed to explain the mechanisms of BRONJ development including: an increased accumulation of bisphosphonates in the jaws due to a high rates of bone turnover; a direct toxic effect of bisphosphonates in the oral mucosa; an altered immune response of the oral tissues to injury or infection; defective wound healing of oral tissues in presence of antiresorptives; inhibition of angiogenesis; long time persistence of BPs in the jaw bone; etc. Since N-BPs accumulate in the skeleton in a dose-dependent manner, it has been also suggested that with prolonged exposure to BPs, local bone accumulation of drug could reach levels that cause cytotoxic effects on bone cells and osteocytes. However, a cytotoxic effect of N-BPs on osteocytes has never been proven at least after therapeutic dosages.

Tooth extraction is considered the most common trigger for BRONJ) [9], followed by apical periodontitis (13.5%) and marginal periodontitis (10.8%) [10]. The intravenous route of administration of BPs can be regarded as a proven risk factor compared to oral bisphosphonates [11]. The cumulative dose, which can be determined by the duration and frequency of administration, is an additional risk factor [12]. However, regarding the etiology of ONJ, various observations must be made which also serve to understand the differences between various drugs used in the treatment of bone pathologies. One of the most considered pathogenetic hypotheses is the inhibition of bone remodeling caused by drugs with anti-osteoclastic activity. Already for this hypothesis there are observations if we consider that other drugs, used with the same indications but with anabolic activity, like romosozumab, may also induce JON.

Romosozumab is a monoclonal antibody with anabolic activity that binds sclerostin, increases bone formation and decreases bone resorption. Also, for this drug cases of ONJ have been reported [13]. This may indicate how inhibition of bone remodeling is not the only reason that may result in ONJ, but perhaps it may concur together with other events. However, in spite of its potential reliability, this hypothesis lacks a histological demonstration, as available data show the presence of active osteoclasts and areas of resorption within necrotic areas [14]. Among BPs we have also to distinguish between N-BP and non-N-BP in addition to considering the different anti-osteoclastic potency that distinguishes them, different permanence in bone, different degree of toxicity toward non-bone cells and even more precisely the differences that exist between N-BP and non-NBP such as clodronate.

Clodronate and ONJ

Clodronate differs from all N-BPs in several characteristics; first, the low affinity for hydroxyapatite (OHA) that results in low drug accumulation in the remodeling-bone areas and a faster elimination from the bloodstream. Clodronate also exerts no toxicity toward the cells of the dental mucosal epithelia and in particular do not affect negatively the keratinocytes, as N-BPs do, therefore do not delay the healing of wounds in the buccal mucosa which can follow dental procedure or pre-existing pathologies. It must be remembered that a defect in the healing of wounds caused in the gingival mucosa is considered a prognostic element of a possible ONJ. It is also known that BPs are characterized by fast bone tropism, long persistence in bone (several years for amino-derivatives, much less for clodronate); the affinity for OHA, varying according to structure with a rank order of zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate [15,16]. The protein binding that is also very low for some N-BP like Zoledronate (22%) and Pamidronate(34%) in comparison to Clodronate; a stronger protein binding may contribute to rendering the BPs less available, during the resorption phase, to spread through the osteocyte canaliculi and negatively impact osteocytes and bone cells which are producers of antibacterial peptides (defensin 1, 2, 3), analogously to osteoblasts, macrophages, dendritic cells and neutrophils [17].

A further pharmacological property that differentiates clodronate from N-BPs is represented by the pro-inflammatory and necrotic effect typical of nitrogen-BPs while clodronate not only has a documented anti-inflammatory activity but can even inhibit that of N-BPs [18]. Other risk factors are an over-suppression of bone remodelling and anti-angiogenic properties, however, local infection of the jawbone seems to play a major role in the pathogenesis of BRONJ. Even considering these additional risk factors, clodronate presents different characteristics compared to N-BPs since it has an antiosteoclastic activity much lower than N-BPs and, except in particular cases, does not reach toxic concentrations for immune cells.

We think it is plausible that in a dental area subjected to a surgical operation like a dental extraction, an implant or as a consequence of severe periodontitis, an inflammatory and an increasing septic process is established due to high presence of N-BPs released by intense osteoclastic activity that follows the inflammatory process due to local damage. We sustain that the primum movens is a severe osteomyelitis, which degenerates into necrosis facilitated by cellular effects of N-BPs and most likely by localized inhibition of mucosal healing, as well as by an initial slowing of the process of microfracture repair, which can allows an abnormal septic and inflammatory phenomenon to readily develop.. In fact, it should be noted that the inflammatory process tends to expand and to infiltrate microfractures, as well as to extending to adjacent areas, determining an interruption of periosteal blood supply. This phenomenon, of great etiopathological relevance, leads, consequently, to a lack of sustenance to the areas involved and the spread of the necrosistic phenomenon [14,19].

Discussion

Although all BPs present a distinct affinity for hydroxyapatite (OHA), to which they are stably bound, they show notable differences in terms of their biological properties and degree of activity, to the extent that they are generally divided into two classes based on the presence or lack of nitrogen, which confers greater biological potency and different degrees of OH-A binding. The presence of nitrogen also lends these compounds a different mechanism of action at the cellular level than compounds without it. Although BPs have been employed in clinical practice for many years and have demonstrated an excellent safety profile, severe ONJ has been described in patients with bone metastases and osteoporosis who were treated with BPs, with cases becoming more frequent as the intravenous use of some particular BPs has become widespread in oncologic practice.

Osteonecrosis of the jaw (ONJ) is defined as exposed, necrotic bone in the maxillofacial region in patients receiving an antiresorptive medication for primary or metastatic bone cancer, osteoporosis, or Paget's disease, without history of radiation therapy to the jaws [20].

Despite a considerable amount of literature addressing BRONJ, the underlying pathomechanism is still unclear. However, several clinical and preclinical studies indicate that a severe inflammation and e deep infection, due to bacteria with the *Actinomyces* species and anaerobic bacteria, seems to have a major role in the pathogenesis of BRONJ. Furthermore, it has been shown that bone loaded with bisphosphonates is more susceptible to infection not only because of the suppression of defense mechanisms, but also because bone loaded with bisphosphonates is more prone to bacterial colonization [21].

It is therefore obvious that the differences existing between BPs, in particular between N-BPs and non-N-BPs (Clodronate), will entail a different degree of risk towards the induction of ONJ. A greater risk is in fact linked to the intravenous use of N-BPs in subjects suffering from tumor pathologies, even if rare cases of ONJ are also described for subjects with osteoporosis. Differently, for clodronate no cases of ONJ have been described in patients with osteoporosis despite millions of patients having been treated and even after long periods of time; in the cases of subjects with bone metastases, only few cases of ONJ have been reported: a case regarding a female patient who took clodronate for almost 13 years for a metastatic bone cancer, she also underwent chemotherapy and radiotherapy [22].

Another case of ONJ is reported for a patient with myeloma who had only been treated with oral sodium clodronate but the risk for osteonecrosis in patients taking oral bisphosphonates, such as Clodronate, was considered uncertain [23]. A few other cases of ONJ, following treatments with clodronate to cancer patients, are mentioned in the scientific literature but without allowing a clear responsibility for the drug. However, it is mandatory to remember that numerous cases of osteomyelitis and osteonecrosis of the jaw are described in subjects exposed to dental therapies such as tooth extraction, dental implants or other dental procedures even without ever having had treatments with BPs. Cases of ONJ are however possible, although rare, after prolonged treatments with N-BPs, both in patients with bone metastases and osteoporosis; such events are instead very rare after clodronate in cancer subjects and unknown or doubtful after oral administration in osteoporosis. The reasons are linked to the different characteristics of the two types of BP. In fact N-BPs have far stronger anti-bone-resorptive effects than non-N-BPs and exhibit direct and potent inflammatory/necrotic effects on soft-tissues. These effects

are augmented by lipopolysaccharide (the inflammatory component of bacterial cell-walls) and the accumulation of N-BPs in jawbones is augmented by inflammation. N-BPs are taken into soft-tissue cells via phosphate-transporters, while the non-N-BPs Clodronate inhibit this transportation. Clodronate has an anti-inflammatory activity while N-BPs are pro-inflammatory [24].

Conclusion

Osteonecrosis of the jaw (ONJ) is a rare but serious adverse event associated with antiresorptive treatment and characterized by persistent, painful necrosis of bone in the maxillofacial region, which reduces quality of life. Mostly described in patients receiving high doses of BPs, as a result of cancer-related hypercalcemia has been also observed in patients receiving lower BP doses for the treatment of osteoporosis. The pathogenesis of ONJ remains poorly understood, and several mechanism have been hypothesized as well as the degree of responsibility attributed to the various BPs, and among them the BPs most responsible were considered those with the highest anti-osteoclastic activity and administered systemically. It is clear, however, that, although antiresorptive activity may be influential, the degree of affinity for hydroxyapatite is also of paramount importance along with the proinflammatory activity shown by certain N-BPs and the lower production of natural antibiotics usually produced by some immunocompetent cells. It is on the basis of these considerations that BPs showed varying degrees of responsibility toward ONJ, and among them clodronate was found to be the least responsible especially toward osteoporotic patients treated even for long periods.

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