Bisphosphonates and bone diseases: past, present and future.

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Editorial

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Bisphosphonates are stable analogues of the naturally-occuring inorganic pyrophosphate and unlike PPi, they are resistant to hydrolysis due to a carbon atom bridging the two phosphonate groups. Whether the first bisphosphonates formerly termed diphosphonates were synthesized in the late 1800s, their clinical applications have been relatively recent. In the 1960s, H. Fleisch and R.G.G. Russell identified the inorganic pyrophosphate as an important physiological regulator of calcification and with M.D. Francis demonstrated that bisphosphonates inhibit the pathological calcifications *in vivo* [1]. These three distinguished researchers will become the leaders of international research on bisphosphonates. The first medical use of the bisphosphonate, etidronate disodium, was in 1968 to treat a young patient suffering from myositis ossificans progressiva. Today, bisphosphonates have been widely used during the last 3 decades in the treatment of diseases involving excessive bone resorption which include post-menopausal osteoporosis, Paget's disease of bone, tumour-associated bone disease, and hypercalcaemia of malignancy. However, it is only in recent years that major advances have been made in our understanding of the cellular and molecular mechanisms of action of this class of drugs. The present issue of Current Pharmaceutical Design, for which I have the honour to be the Executive Guest Editor, will give an overview of the past, the present and the future of bisphosphonates. This special issue prepared by specialists of bisphosphonates addresses all aspects of bisphosphonates including their pharmacology and chemical evolution, their recent elucidated mechanisms of action (in bone and non bone cells), the assessment of their biological activities, their main pre-clinical and *in fine* their main clinical applications.

The specific pharmacology of nitrogen-containing bisphosphonates (N-BPs) is mainly attributable to their calcium adsorption and chelating properties. In agreement with this specificity, they primarily affect the function of resorbing osteoclasts but recent advances gave some evidences that other cell types (osteoblasts, osteocytes, monocytes, T lymphocytes, etc) could be the targets of these drugs. In this context, A. Roelof, K. Thompson, F.H. Ebetino, M.J. Rogers, and F.P. Coxon give an overview of the pharmacology of bisphosphonates covering their development, molecular mechanisms of action, bone mineral binding properties and cellular actions [2]. Once bound to bone the N-BPs can be internalized by osteoclasts

where the drug can then interact with its molecular target, the Farnesyl Pyrophosphate Synthase (FPPS), a key enzyme in the mevalonate pathway. This targeting then prevents the prenylation process, disrupts vital signaling and induces the loss of osteoclast activities and their death. Recent investigations summarized by J.E. Dunford [3] clarified the biochemistry of FPPS and its inhibition by the N-BPs but also identified many other targets for this drugs (other FPPS enzymes, Matrix Metalloproteinases, Protein Tyrosine Phosphatases, etc). These new targets lead to the development of a new generation of N-BPs characterized by a low affinity to the bone mineral and then can be available to extraosseous targets. These observations opened novel clinical applications. FPPS is the main targets of N-BPs, however these drugs exert consequently very large effects on cell metabolism affecting cell adhesion, migration, division and death. To identify the mechanisms of actions of bisphosphonates, novel methodologies have been set up. L.M. Mitrofan, S. Auriola, H. Mönkkönen and J. Mönkkönen [4] present an original review which highlights the main methodologies used to monitor the action of BPs in *in vitro* cell models, with a special emphasis on the detection of BP-induced ATP-analogues by mass spectrometry. Cell death monitoring, immunomodulatory effects and inhibition of growth/proliferation are also described.

Bisphosphonates have been used successfully for many years to reduce the skeletal complications associated with the benign and malignant bone diseases that are characterized by enhanced osteoclastic bone resorption. Until recently, it was thought that the clinical efficacy of bisphosphonates in the treatment of cancer patients with bone metastases was purely a result of the inhibition of osteoclast-mediated bone resorption. However, recent studies have demonstrated that bisphosphonates inhibit the growth, attachment and invasion of cancer cells in culture and promote their apoptosis. These results suggest that these drugs are also anti-cancer agents, raising the possibility that they could inhibit cancer-cell colonization in visceral organs. Thus, a series of complementary reviews addressing the clinical interest of bisphosphonates in oncology is proposed in the present issue. The first is proposed by G. Moriceau, B. Ory, B. Gobin, F. Verrecchia, F. Gouin, F. Blanchard, F. Rédini and Heymann D. and describes the clinical applications of bisphosphosnates in the primary bone tumors (giant cell tumor of bone, osteosarcoma, Ewing's sarcoma, chondrosarcoma, etc.) [5]. Thus, these drugs have been used as a carrier for radio nucleotides to develop novel approaches of bone imaging. They exert also indirect anti-tumour activities *in vivo* by interfering with the bone microenvironment and target osteoclasts, endothelial cells and immune cells (tumour-associated macrophages, γ9δ2 T cells). They induce tumour cell death *in vitro* and similar activity is suspected *in vivo* explaining why clinical trials assessing the

combination conventional chemotherapy with bisphosphonates are actually in progress. In contrast to primary bone tumors for which the clinical impact of bisphosphonates is currently in progress, bisphosphonates are now a standard treatment for bone metastases. Pre-clinical data demonstrated the anti-tumor effects of bisphosphonates alone and to combine theses drugs with other anti-cancer agents. S.P. Syddall, P.D. Ottewell and I. Holen give an overview of these pre-clinical studies and of the main clinical studies which aimed to determine whether adding bisphosphonates to standard anti-cancer therapy will improve outcome for patients [6]. E.J. Woorward and R.E. Coleman have perfectly completed this last review and compelled the most recent reported randomised clinical studies to support the use of bisphosphonates in clinical practice at earlier stages of the disease to prevent bone metastases [7]. Recent data revealed that N-BPs are able to stimulate human γδ T cells and pastes N-BPs at the crossroad of innate and adaptive immunity. This new activity of N-BPs strengthens their interest as anti-tumour agents through the modulation of immune system. This novel activity of N-BPs is summarized by P. Clézardin and M. Massaia in an exhaustive review on the molecular and cellular mechanisms by which N-BPs stimulate the expansion and cytotoxic activity of human γδ T cells [8]. They also discuss the emerging clinical evidence that N-BPs can have a role in cancer immunotherapy. It will be not objective to focus all reviews of this issues to discard the other therapeutic options for the treatment of bone metastases excepted N-BPs. The recent better understanding of bone biology lead to the elaborations of newer and more and more efficient drugs with requires very stringent clinical studies to prove their clinical interest and to determine the long term side-effects. J.T. Buijs, CC.H. Kuijpers and G. van der Pluijm described in details the molecular process of metastasis from primary tumor to bone through which the novel drugs have been elaborated [9]. These authors have checked the novel therapeutic targets (bisphosphonates, RANKL, TGFβ, Wnt pathway, MMPs, Cathepsin K, integrins, calcium sensing receptor, CXXR5/CXCL12 axis, ET-1 pathway, glcycoprotein nonmetastatic B, Src, etc) and the strategies developed for the treatment of bone metastases. To complete this very large panel of review on bisphosphonate and cancers, M.A. Lawson, J. Ashcroft and P.I. Croucher have proposed a specific review on multiple myeloma and bisphosphosnates [10]. Indeed, multiple myeloma is an incurable B cell neoplasm often resulting in devastating osteolysis. Bisphosphonates have been successfully used to treat the tumour-induced bone disease associated with multiple myeloma. Their review focus on preclinical studies and clinical investigations of patients suffering from

multiple myeloma which have contributed to a better under understanding of the mechanisms of action of bisphosphonates in this pathology.

Because bisphosphonates currently remain the principle drugs used to treat excessive bone resorption, they have extensively used in rheumatology. The first review on this topic, prepared by B. Le Goff, P. Guillot, J. Glémarec, J.M. Berthelot and Y. Maugars summarize the use of bisphosphonates for the treatment of osteoporosis and compared their clinical effects with other treatment [11]. They have done an evaluation of the cost of all treatments, topic particularly important in the actual health politics. The second review presented by **B.** Le Goff, J.M. Berthelot, Y. Maugars and E. Romas focuses on the new potential alternative indications for bisphosphonate in rheumatic diseases [12]. Indeed, bisphosphonates could also have others properties through a specific analgesic or anti-inflammatory effect. Thus, rheumatic diseases like rheumatoid arthritis, spondylarthritis or SAPHO syndrome that are associated with bone loss could be good candidates for bisphosphonate therapy similarly to other non-inflammatory rheumatic diseases like bone osteonecrosis, algodystrophy, fibrous dysplasia or neuropathic osteoarthropathy.

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