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Clodronate : A Potential DMOAD in Osteoarthtitis

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Abstract

Osteoarthritis is an inflammatory-degenerative joint disease that affects the osteochondral unit with the concomitant intervention of the immune system; this causes pain and progressive functional limitation. With a varied and complex etiopathogenesis, Osteoarthritis has a subtle outcome and an inexorable evolution towards joint deformity. The therapeutic approach makes use of non-pharmacological and pharmacological aids. Pharmacological therapy consists of symptomatic drugs that act on acute and especially chronic pain, in an attempt to decrease the incidence of any structural damage to the cartilage and subchondral bone. If the anti-resorptive drugs cure the subchondral-epiphyseal osteometabolic pathology, the interventions on the cartilage have not produced important and well evaluable results, even after prolonged therapies. This contribution analyzes the profile of Clodronate, used for the treatment of subchondral bone edema in Osteoarthritis, regarding its potential protective effects in cartilage, like DMOADs.

Keywords: Osteoarthritis, Osteochondral Unit, Bone Edema, Chondropathy, Clodronate

Introduction

For several decades pharmacologists and clinicians have been researching and evaluating different therapeutic approaches in an attempt to find a remedy to that disabling pathology that has always accompanied man, almost a corollary inextricably linked to advancing of his age: Osteoarthritis (OA).

OA presents itself in a subtle way, slowly without striking warning signs except some warnings that are often totally ignored both for their intermittency and for the lack of effective drugs. On this respect, the placebo effect, carried out by harmless substances, is also well known and has often compromised the reliability of many experimental results. In fact, OA has a very complex etiology where numerous genetic and environmental events, lifestyles or traumas have a role and where the cartilage structure and sub-chondral bone play a decisive role with the concomitant intervention of the immune system. Due to the OA complexity, it remains difficult to intervene both in a preventive or curative way, even if the latter aspect is what has been most, if not exclusively, followed and it still is for this reason that any therapeutic approach has been addressed to the treatment of acute symptomatic conditions followed by a chronic treatment in an attempt to repair any structural damage to the cartilage and subchondral bone.

If with the availability of anti-resorptive drugs it was possible to intervene on the bone structure thanks to its dynamism, its vascularity and innervation, the intervention on the cartilage not led to important and well assessable results, even after long therapies.

Clodronate and Cartilage

One of the reasons, if not the most important reason, of the interventional difficulties lies precisely in the structure of the articular cartilage, suitable for the function to be carried out, but whose cells, the chondrocytes, are difficult to access, embedded in a dense structure of collagen fibers immersed in a matrix of glycoproteins and polyanionic proteoglycans which, if they can allow the passage of nutrients from the synovial fluid are less permeable by large molecules or by drugs. The lack of its own vascular system and innervation account for this difficulty and the fact that any damage is not perceived as painful or as warning signals. Furthermore, chondrocytes have a trilaminar membrane, are surrounded by a double matrix rich in polyanionic substances and do not communicate with other chondrocytes, except in some areas of the cartilage structure. Chondrocytes are rather torpid cells whose repairing activity requires times that are not well specified, but in any case, very long and needing adequate stimuli.

The numerous studies that have followed over the time have aimed at identifying substances that could stimulate a restorative intervention by cultured in vitro chondrocytes in order to be able to precisely control any increase in the productivity of the cells themselves.

Preliminary studies concerned with the structure of joints and their composition, the synthesis and the mechanism of cartilage destruction, followed by investigations on the effects of different compounds on the synthesis by articular chondrocytes [1].

Among the different compounds investigated a special attention was dedicated to the Bisphosphonates (BPs) due to the confirmed activity of these compounds as inhibitors of bone resorption and the capability of preventing or limiting the subchondral bone sclerosis.

Of the various BPs studied, Clodronate (dichloromethylidene-bisphosphonate) (CLO) has been shown to exhibit high biological activity increasing the uptake of α-amino-isobutyrate by isolated chondrocytes as well as the synthesis of sulphated extracellular macromolecules secreted by the cells into the peri-cellular space and into the growth medium [2]. The stimulatory effect was dose-dependent and the increment in proteoglycan synthesis was still evident with cell that were exposed continuously to the CLO in primary as well as secondary culture suggesting the persistence of the effect for long period of time.

The same group of investigators, in a different study [3], assessed the effects of CLO on the synthesis of collagen by isolated rabbit articular chondrocytes and bone cells and by isolated rat clavaria bone cells. The study showed that CLO causes articular chondrocytes to **increase collagen biosynthesis** and the increment was also evident with cells that were exposed continuously to CLO in the primary and secondary culture. The synthesis of collagen by isolated bone cells was also increased as well as by bone explant from rat treated with 1 and 10 mg of P/kg of CLO subcutaneously.

The increment in the synthesis of collagen, with the concomitant increase in proteoglycans, suggests that total extracellular matrix formation became enhanced by the influence of clodronate.

However, it should be pointed out that the cells apparently have to be exposed to the bisphosphonate for more than 24h in order to respond. These results are in sharp contrast with those of studies performed by Guenther et al. (1979), where it was shown that the synthesis of proteoglycans became stimulated within 24h after addition of the bisphosphonate to the growth medium [3].

In the same studies a different bisphosphonate,1-hydroxyethane-1,1-bisphosphonate (HEBP) was used as comparison drug, but this last resulted always without activity, giving the idea that the efficacy is linked not to the P-C-P side, common to all the BPs, but on the kind of side groups of the molecule (the two chlorine atoms). Moreover, the studies in vivo on the biosynthesis of collagen suggest that the effect is present also when clodronate is administered to living animals.

Only recently the effects of CLO on chondrocytes have been reviewed and in a paper of Valenti et al. (2017) the six months i.m. treatment with 200 mg of CLO weekly in OA patients was able to stimulate MSCs maturation toward the chondrogenic lineage [4]. CLO strongly increased SOX9 expression after three- and six-months treatment, compared to patients 'basal value'. In addition, after six months of treatment, patients '*SOX9* and COL2A1 expression exceeded normal donors. Transcription factor *SOX9* induces mesenchymal cells differentiation into chondrocytes, upregulating specific chondrogenic genes such as COL2A1 [5]. Similar data have been obtained in an in-vitro study strengthening the idea that CLO stimulates chondrogenic differentiation of precursors and may hinder effectively the pathogenesis and progression mechanisms of OA.

A further in-vitro study strengthen the anabolic effect of CLO (100 microM) on chondrocytes with the stimulation of the synthesis of cartilaginous extracellular matrix collagen and proteoglycans (13% and 14%), as determined by radiolabeled incorporation. However, there was a sustained effect with 89-90% increase in proteoglycan and collagen content in CLO treated cultures observed over the long term. In the same study a different BP, the amino derivative Pamidronate, had no apparent effect on ECM synthesis. The study demonstrates that CLO induces an anabolic effect in chondrocytes and the response appears to be mediated by export of an intracellular ATP-analog which then signals through the membrane purinergic receptors without changing the chondrocyte phenotype [6].

CLO is a non-nitrogen containing bisphosphonate and it has been shown to be metabolized inside the cells into a non-hydrolyzable ATP analog, adenosine 5′ (β, γ-dichloromethylene) triphosphate (AppCCl2p) [7], due to the similarity between ATP and AppCCl2p it is conceivable that this metabolite could interact with membrane purinergic receptors leading to anabolic response. After the uptake by fluid-phase endocytosis, CLO is metabolized into AppCCl2p which is released through hemi-channels, pannexin and connexin, and stimulate P2Y, P2X receptors with the result of an anabolic effect on the chondrocytes (Figure1). In spite of the suggesting mechanism of action proposed for CLO, the generation of the metabolite AppCCl2p inside chondrocytes, albeit possible, has been not demonstrated, however previous studies have demonstrated that purinergic receptors agonists (e.g., ATP) elicit an anabolic response in both bovine and human chondrocytes under similar concentrations to the bisphosphonate concentrations used in the present study [8].

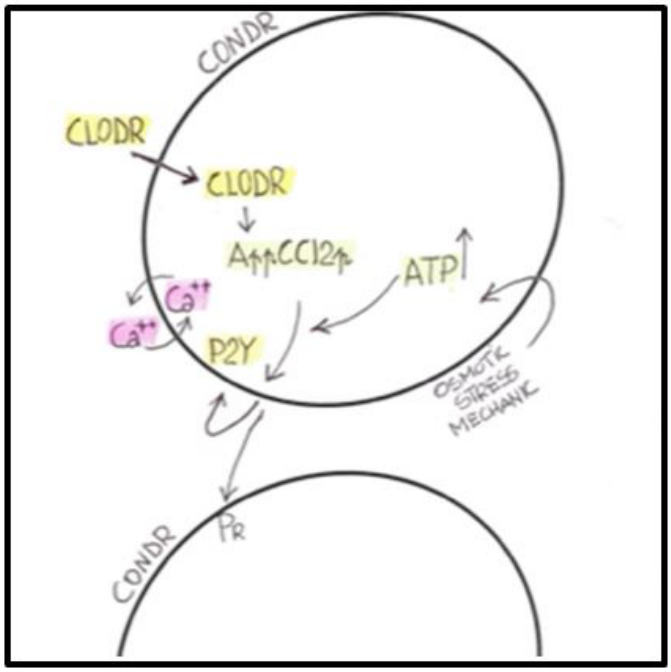

Figure 1: Clodronate action mechanism: CLO is metabolized into AppCCl2p which is released through hemi-channels and stimulate P2Y receptor with final anabolic effect on the chondrocytes

There is also uncertainty related to the levels of CLO in cartilage achieved *in vivo*. However, previous studies involving intra-articular injections of CLO showed positive effects of CLO with doses in the range of 10-4 to 10-3M [9] which were comparable to levels in which anabolic effects on chondrocytes were observed.

This proposed mechanism of action may be also one of several through which bisphosphonates might ameliorate cartilage damage. For example, bisphosphonates also bind and inactivate basic calcium phosphate crystals, which are common mediators of articular destruction in damaged joints [10].

The implication of the purinergic system in the chondrocytes activation is also reported in a paper of Pingguan-Murphy et al. This study investigates the influence of cyclic compression on intracellular Ca2+ signaling using the chondrocyte-agarose model. Cyclic compression modulated global Ca2+ signaling by increasing the percentage of cells exhibiting Ca2+ transients (population modulation) and/or reducing the rise and fall times of these transients (transient shape modulation). The frequency and strain rate of compression differentially modulated these Ca2+ signaling characteristics, providing a potential mechanism through which chondrocytes may distinguish between different loading conditions. The cyclic compression appears to activate a purinergic pathway involving the release of ATP followed by the activation of P2 receptors causing a combination of extracellular Ca2+ influx and intracellular Ca2+ release and modulating the cartilage homeostasis [11]. Other papers have confirmed that ATP has a role in the response of chondrocytes to mechanical stimulation via P2Y2 purineceptors [12, 13].

Discussion

The above data tend to confirm the importance of the purinergic system and the role of the chondrocyte ATP in the transmission of signals stimulating chondrocyte activity. CLO can enter into this mechanism as it is able to enter chondrocytes through phosphate channels and be metabolized in the analogous AppCCl2p of ATP to perform an anabolic action similar to that of ATP itself. However, it is of fundamental importance to know if CLO is able to reach the chondrocyte cells embedded in the matrix and to remain in contact for a time sufficient to stimulate the purineceptors.

This last aspect would seem to be confirmed both by the results of the studies on OA patients treated both intramuscularly [14,15] and intraarticularly as well as by kinetic studies with labeled CLO injected i.a. in rats. In this last study, it was found that CLO enters the cartilage widely and remain included for a very long time and in the order of several weeks. All this seems to confirm the possibility of using CLO in the therapy of OA not only for its anabolic activity on chondrocyte but also for its confirmed anti-inflammatory and pain-reliving activity.

OA is now rightly considered not only a disease of articular cartilage, but of the osteochondral unit, i.e., the complex of cartilage and subchondral bone, mediated by endoarticular inflammatory cytokines that overcome the tidemark attacking the underlying spongiosa leading to a phenotic expression of osteoporosis, unlike cases with greater mechanical expression with sclerotic phenotype. [16]. Such suffering of the osteochondral unit already occurs in the starting of the disease and certainly in its evolution in aggravation. In this context, the therapy of chondropathy is nowadays supported by that of epiphyseal subchondral bone edema [17]. The use of BPs and of Clodronate in particular in this last condition represents now an acquired fact in the osteometabolic management of OA. CLO is expressed with its three synergistic positive effects: antiresorptive, anti-inflammatory, and pain-relieving.

The studies described above have highlighted a further therapeutic effect to the benefit not only of the bone but also of the cartilage as a target of OA, in a chondrotrophic sense, with a potential completeness of therapeutic activity increasing the hope of curing this complex disease in a more incisive way. The significance and specificity of this new therapeutic perspective of CLO deserve further studies, in addition to the pilot ones highlighted.

However, adequate RCTs studies are needed to verify whether the use of CLO can be placed as a disease-modifying drug (DMOAD) or only as a symptomatic drug.

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