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Review

Bisphosphonates and osteoarthritis

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Osteoarthritis (OA) is the most common degenerative joint disease; it represents a major public health problem and is ranked among the top 10 causes of disability worldwide, especially in elderly subjects. Although the main characteristic of OA is the progressive degeneration and loss of joint cartilage, it is now commonly accepted that all the articular components are involved, as the structural alterations observed in OA include sub-chondral bone changes, osteophyte formation, variable degrees of synovial inflammation, degeneration of ligaments and hypertrophy of the joint capsule. There are currently no treatments that delay or halt OA progression; in general, therapeutic agents that modulate the cellular activities in individual joint tissues such as bone, cartilage or synovium have proven to be effective in arresting or slowing the progression of joint pathology in animal models of OA. Particularly, bisphosphonates may determine some positive structural and symptomatic effects in the treatment of OA through different mechanisms, including their ability to modify osteoclast and osteoblast metabolism in the sub-chondral bone and to inhibit the synovial inflammatory changes.

Key words: Bisphosphonates, Osteoblast, Osteoclast, Osteoarthritis, Inflammation

BACKGROUND

Osteoarthritis (OA) is the most common degenerative joint disease and represents a major public health problem. OA is ranked among the top 10 causes of disability worldwide, especially in elderly subjects. Major features of OA include chronic pain, joint instability, stiffness and radiographic joint space narrowing. Although the main characteristic of OA is the progressive degeneration and loss of joint cartilage, it is now commonly accepted that all the articular components are involved, as the structural alterations observed in OA include sub-chondral bone changes, osteophyte formation, variable degrees of inflammation of the synovium, degeneration of ligaments and hypertrophy of the joint capsule [1,2]. The sub-chondral bone undergoes structural changes that affect the overlying articular cartilage, such as increased thickness of the cortical plate, changes of mass, architecture and mineralization of the bone, development of bone cysts and growth of osteophytes at the joint margins. Nevertheless, the exact relationship between the changes in the sub-chondral bone and other osteoarthritic events has yet to be fully elucidated and controversy exists regarding the timing and sequence of the pathological changes.

The mechanisms responsible for the pathogenesis of sub-chondral bone changes in OA are still unclear, but many clinical and experimental evidences suggest that both osteoblasts and osteoclasts can be involved. It has been clearly demonstrated that osteoblast-like cells isolated from sub-chondral bone of osteoarthritic patients have abnormal metabolic activity [3-6]. Decreased bone mineral content and decreased number of trabeculae in sub-chondral bone structure in the early OA stages have been observed by magnetic resonance imaging [7] and high-turnover type bone metabolism derangement has been considered as a possible cause of OA [8].

An increasing number of experimental and clinical data suggests that the impairment of sub-chondral bone is crucial to the development and progression of OA. Many studies support the hypothesis that the skeletal adaptations can antedate detectable alterations in the structural integrity of the articular cartilage [9]. Despite the

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protection of cartilage has traditionally been the main focus of research, the sub-chondral bone has become a potential therapeutic target in OA.

There are currently no treatments that delay or halt OA progression; in general, therapeutic agents that modulate the cellular activities in individual joint tissues such as bone, cartilage or synovium have proven to be effective in arresting or slowing the progression of joint pathology in animal models of OA [10]. As an impairment of the sub-chondral bone turnover occurs in OA, it has been postulated that treatments that can modulate bone remodelling, such as Bisphosphonates (BPs) could become a disease-modifying therapy. BPs are anti-resorptive agents that inhibit the recruitment and maturation of osteoclast precursors and the activity of mature osteoclasts in the bone [11]. These drugs have been used for decades in clinical practice for the treatment of bone diseases characterised by an increase of bone remodelling processes, in particular post-menopausal and glucocorticoid induced osteoporosis, Paget's disease, multiple myeloma and bone metastases. BPs have more recently been proposed as potential drugs able to modify the natural history of OA by preventing the loss of structural integrity in the subchondral bone compartment [12].

EXPERIMENTAL DATA AND ANIMAL MODELS

It has been shown that BPs prevent the development of bone alterations in animal models of OA and exert a chondroprotective effect, but their direct effects on chondrocytes function are not clearly known [13 14].

Besides their inhibitory effects on the maturation and activation of the osteoclasts, BPs also influence osteoblasts *in vitro*, by affecting their differentiation, proliferation, migration and cytokine expression. It results in either stimulatory or inhibitory effects, depending on the dosage and the kind of BPs used [15-23]. Nevertheless, very few studies have assessed the ability of BPs to modify *in vitro* the metabolic activity of the sub-chondral osteoblasts in OA joints [24 25].

The treatment with alendronate of human osteoblasts obtained from OA patients led to a significant increase in the level of expressed RANKL mRNA and RANKL/osteoprotegerin mRNA ratio, due to an increased expression of RANKL without any effect on osteoprotegerin mRNA expression or osteoprotegerin secretion [25]. Nevertheless, other data showed that BPs did not stimulate the synthesis or the expression of any proteins in the sub-chondral osteoblasts. Moreover, high doses of BPs may inhibit the osteocalcin synthesis in these cells [24].

Other experimental studies evaluating the effectiveness of bone anti-resorptive agents for OA have shown promising results on animal models. Some data support the hypothesis that BPs may reduce the progression of osteophyte formation and the sub-chondral bone resorption.

The preventive use of alendronate has been investigated in a rat model of severe OA, in which decreased trabecular bone volume fraction (BV/TV), development of sub-chondral sclerosis of the tibia and progressive loss of cartilage were induced by the combination of moderate exercise, over a 6 weeks period, together with weekly intra-articular injections of papain in the knee during the first 3 weeks. A mild increase of trabecular thickness and an improved preservation of both BV/TV and cartilage extracellular matrix compared to the control group were observed in the rats treated with alendronate 12 weeks after the beginning of OA induction. Nonetheless, alendronate had no effect in reducing the sub-chondral bone sclerosis during OA progression. Furthermore, alendronate significantly decreased bone remodeling, reduced osteophytosis, protected the cartilage extra-cellular matrix from degradation, improved the content of glycosaminoglycans in the cartilage and reduced the synovial macrophage activation [26].

Other studies on different animal models of OA showed that alendronate markedly reduced cartilage lesions and delayed cartilage degeneration, showing a chondroprotective effect. In animals treated with alendronate, the formation of osteophytes was suppressed and fewer microscopic alterations of the cartilage were shown in comparison to the placebo group, in which various degrees of fibrosis, cracks, cell loss and multicellular chondrocyte clusters were observed. Furthermore, alendronate reduced cartilage neoangiogenesis and the expression of matrix metallo-proteinase 13 (MMP-13), interleukin-1β (IL-1β), vascular endothelial growth factor (VEGF), RANKL and markers of cartilage degradation, such as serum cartilage oligomeric matrix protein (COMP), urinary C-telopeptide of type II collagen (CTX-II) and type-X collagen. On the other hand, the Bone Morphogenetic Protein 2 (BMP-2) expression increased after treatment with BPs. In the sub-chondral bone, alendronate induced a significant increase of hystomorphometric parameters of bone formation (bone volume fraction, trabecular bone thickness, trabecular number) with a reduction of markers of bone resorption (trabecular separation) [27-31].

In a rat model of OA induced by glycolysis inhibitor, the intra-articular administration of zoledronic acid significantly reduced pain and attenuated or prevented the degeneration of bone and cartilage [32]. In a rat model of knee OA induced by anterior cruciate ligament transection, animals treated with systemic high dose of zoledronic acid showed milder macroscopic ulcerations of cartilage, lesser cartilage softening and fibrillation,

without complete disorganization, when compared to rats treated with placebo; the microscopic morphology of the articular cartilage was better in the zoledronic acid treated rats, with only a partial disorganization of the matrix and with presence of proliferating chondrocytes, indicating on-going cartilage repair and regeneration process. Hypocellularity was the prevalent finding in the placebo group [33]. In rats treated with intra-articular zoledronic acid, the histological cartilage score was higher compared to placebo and indicated that the progression of synovitis (in terms of inflammation and necrosis) was significantly lower [34]. In the same experimental animal model of OA, pamidronate prevented or even reversed cartilage damage, inducing an increase of chondrocytes and extra cellular matrix, reducing fibrosis of cartilage surface [35].

CLINICAL STUDIES

In controlled clinical trials and in open label clinical trials, BPs showed to be effective in the treatment of pain and in the treatment of impaired function and radiographic joint progression in OA patients. Two large randomised controlled studies have been performed to assess the efficacy of risedronate in patients with knee joint OA. In a 1 year prospective, double-blind, placebo-controlled study (BRISK), a total of 285 patients with mild to moderate knee joint OA were randomized to receive once-weekly risedronate (5 mg or 15 mg) or placebo. Besides the reduction of markers of cartilage degradation and bone resorption, a weekly dose of 15 mg risedronate significantly improved the global assessment score, reduced the walking aids and determined a significant improvement in the Western Ontario and McMaster University (WOMAC) pain score after 12 months of treatment when compared to the placebo group. No evident effects were achieved in the group of patients treated with 5 mg weekly risedronate. No significant differences were found in the intervention groups concerning the radiographic joint space narrowing. Only 8% of the OA patients in the placebo group had detectable progression of the disease [36].

These results were not confirmed by two parallel multicentre randomized, double-blind, placebo-controlled phase III studies performed in North America and Europe (KOSTAR). Placebo or risedronate in different doses (5 mg/day, 35 mg/week or 50 mg/week) were given during 2 years to a total of 2483 randomised patients [37]. In both the studies, no significant differences in the mean change from baseline in pain scores and on patient global assessment score (WOMAC) between treatment groups were found. Similarly, no significant difference in radiographic progression was reported. Only 13% of the OA patients receiving placebo showed a significant radiographic progression over the 2 years follow-up. It can be speculated that this large clinical trial was underpowered based on the low rate of OA progression in the placebo group.

As expected, in both the North American and European groups, a dose-dependent decrease in the levels of markers of bone resorption and cartilage degradation (urinary CTX-II) with risedronate was observed within 6 months and continued through 24 months; interestingly, in a sub-analysis, it was demonstrated that in subjects with accelerated cartilage degradation at baseline, the biochemical response after 6 months of risedronate use was associated with a significant reduction in radiological progression compared to subjects with no response in CTX-II levels [38]. The further analysis of the subgroup of patients with significant radiographic progression of joint space narrowing showed that, in comparison to the placebo group, the trabecular structure was better retained in patients treated with risedronate 15 mg/week and an improved trabecular number was found in the group of patients treated with 50 mg/week dose of risedronate over 2 years, with a preservation of the structural integrity of the subchondral bone [39].

A phase 2 randomized, partially blind clinical trial evaluated the efficacy of different dosages (0,5 mg or 1 mg or 2 mg once a week for 4 weeks; 1 mg twice a week for 2 weeks) of intra articular clodronate *vs* hyaluronic acid (20 mg once a week for 4 weeks) in patients with primary knee OA. No statistically significant differences in pain or mobility scores were reported during the initial five weeks of treatment between the groups. After adjusting for multiple comparisons and paracetamol use, the authors reported a significant reduction of pain in patients treated with 1 mg clodronate compared to the hyaluronic acid group [40].

Kawasaki et al. evaluated the additive effect to therapeutic exercise of risedronate 2,5 mg/day or glucosamine compared to exercise alone in patients with knee OA. After 18 months, a significant improvement in pain was found in all the treatment groups, but no significant differences between the groups concerning the functional outcomes, pain and joint space width were observed [41].

The effect on pain and bone marrow oedema (MRI) of a single intra-venous injection of zoledronic acid 5 mg was compared to placebo in patients with knee OA in a randomized controlled trial. Zoledronic acid induced a significant improvement of pain after six months of treatment, but not after three or twelve months. A reduction in total bone marrow oedema was also reported after 6 months in the zoledronic acid group [42].

An open randomized pilot trial evaluated the efficacy of intra-venous clodronate compared to

hydroxychloroquine for the treatment of erosive OA of the hands. A significant reduction of pain scores and a significant improvement of functional scores and patient's global assessment were found in patients treated with clodronate at 12 months, whereas hydroxychloroquine resulted to be ineffective [43].

One clinical trial, performed on a small case-series, assessed the use of alendronate in symptomatic hip OA. Patients were randomly assigned to receive alendronate 35 mg/weekly and calcium lactate 600 mg/daily or calcium lactate alone for 2 years. Alendronate induced a significant reduction of pain at 12 months, whereas the control group showed worsening of pain; nevertheless, the prevention of OA radiographic progression was not observed neither in alendronate treated patients, nor in placebo group [44].

The effect of clodronate was assessed in a double-blind, randomized placebo-controlled trial in which patients with symptomatic knee OA were randomized to receive intra-articular injection of 2 mg clodronate or placebo for 4 weeks. Clodronate treatment significantly reduced pain scores and improved the Lequesne functional index, which was associated to a reduced analgesic consumption compared to placebo [45].

A randomized, double-blind, placebo-controlled study assessing the efficacy of i.v. neridronate in controlling pain in patients with acute painful knee OA showed that intra-venous neridronate 100 mg daily for 10 days significantly reduced pain and improved quality of life compared to placebo; further, the bone marrow lesions evaluated by MRI showed a significant decrease only in neridronate group [46].

In a cross sectional study the effects of alendronate and other anti-resorptive drugs (oestrogens and raloxifene) on the structural features of knee OA in elderly women, assessed by magnetic resonance imaging and radiography, and on the severity of symptoms, were compared [47]. No significant association between overall use of anti-resorptive drugs and the presence of knee pain and radiographic changes of OA of the knee were found. Nevertheless, alendronate, but not oestrogens, was associated with less severe knee pain. Whilst there was no statistically significant difference between the intervention groups in WOMAC pain score, a statistically improved scores in the alendronate group compared to the no-treatment group was observed. Both alendronate and oestrogens were associated with significantly fewer sub-chondral bone attrition and bone marrow abnormalities of the knee, as assessed by MRI, suggesting a potential structural effect on knee OA.

The Fracture Intervention Trial (FIT) [48] is a large randomised study that evaluated the anti-fracture effect of alendronate versus placebo over 4 years in post-menopausal women. A subgroup of 200 participants in this study was randomly selected for further radiographic analysis focusing on features of spinal OA, in order to examine the effects of alendronate on the progression of spinal disc degeneration compared to placebo group. The adjusted mean change in osteophyte score in the alendronate treatment group was lower compared to the placebo group. Nevertheless, the spinal radiographic changes were subtle, with minor clinical relevance, as acknowledged by the investigators. The adjusted mean changes in disc-space narrowing were also lower in the alendronate group than the placebo group, but the difference did not reach a statistical significance [49].

In the analysis of data from the Osteoarthritis Initiative (OAI) the effects of potential benefits of BPs over a number of years were evaluated. The investigators aimed to examine the effect of long-term (up to 4 years) BPs use on OA symptom and structural outcomes in people selected from the OAI cohort, a multicentre population-based observational cohort study of knee OA. Patients with clinical OA in early stages with poor prognosis were included and grouped in those not using bisphosphonates and those who used the drugs for other purposes (treatment of osteoporosis or Paget's disease). Differences between users and non-users in knee pain severity scores, WOMAC score and radiographic joint-space narrowing at each annual time point were assessed. A significant decrease of the numerical scale ratings of pain was observed after 2 and 3 years, but the effect had declined by year 4. Nonetheless, the WOMAC pain scores in BPs users were not significantly lower than the non-users. Only a trend towards less joint-space narrowing by year 4 was observed in patients using bisphosphonates compared with those not using the drugs [50].

Overall, the available data from clinical studies, showed that BPs are effective in terms of reduction of joint pain and stiffness and in improving function, although their effect on OA structural changes and progression are controversial [51].

CONCLUSIONS

BPs may determine some positive structural and symptomatic effects in the treatment of OA through different mechanisms. BPs may affect osteoclast and osteoblast metabolism in the sub-chondral bone, reducing the high bone turnover mediated by osteoclasts and by inducing an anabolic effect on osteoblasts. Further, BPs may benefit the OA joints by inhibiting the synovial inflammation, which is associated with both symptoms and structural damage progression [52 53]. Even if many studies showed a positive effect of various BPs

on different clinical and structural findings of OA, the real effectiveness of these drugs as disease modifying therapy is not clearly established. A number of methodological weaknesses, such as the heterogeneity of patients, the different stages of disease of recruited patients, the small-size of case-series, and the lack of evaluation of bone and cartilage lesions by using standardized scoring system limit the scientific value of the mentioned studies. Nevertheless, further clinical studies could confirm the usefulness of BPs for treatment of OA, considering the well-known pain-relieving anti anti-inflammatory effects of these drugs and the key role played by subchondral bone in the pathogenesis of OA

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