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EDITORIAL

USE OF CLODRONATE IN THE MANAGEMENT OF OSTEOARTHRITIS: AN UPDATE

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Osteoarthritis (OA) is a chronic rheumatic disease characterized by joint cartilage wear and loss of normal function. Clodronate (CLO) is a first-generation non-nitrogen-containing bisphosphonate that exerts anti-inflammatory and analgesic and modulatory effects on bone and cartilage metabolism. To date, few clinical studies have evaluated the effect of CLO in OA. Current evidence suggests that CLO may represent a new type of analgesic drug as it reduces pain in bone diseases characterized by edema such as Complex Regional Pain Syndrone type-1 and vertebral fractures. Thanks to its anti-inflammatory and analgesic effects, CLO has been shown to afford benefit in knee OA, erosive OA of the hand, painful knee hip prosthesis and veterinary practice. Transforming growth factor β1 has also been found to play an important role in the pathogenesis of OA. The present review article examines recent evidence on the potential use of CLO in the treatment of OA.

Osteoarthritis (OA) is a slow progressive disabling and painful disease affecting whole joints, with inflammation involving the synovia, tendons and soft tissues. However, the pathogenesis of OA is still not completely understood, but in the past twenty years the role of subchondral bone has been shown to be crucial. Indeed, there is a functional link between articular cartilage and subchondral bone, which provides mechanical support during joint movements and is able to adapt itself to different load changes. Moreover, cartilage, subchondral bone and the nearest soft tissues form a functional and biochemical unit where cartilage and bone can communicate over the calcified tissue barrier.

Magnetic resonance imaging has demonstrated that early changes in subchondral bone (increased bone turnover, subarticular osteoporosis, microfractures and microcracks) can precede OA lesions and that subchondral bone loss is correlated with pain and subsequent cartilage loss (1, 2).

Few treatment options are currently available that can alter the course of OA. Current treatment guidelines include pain control with oral or topical analgesic drugs (e.g. NSAIDs, opioids, capsaicin) accompanied by physical therapies to maintain function. Bisphosphonates (BPs) are anti-resorptive agents (currently used in the treatment of osteoporosis). BPs have emerged as a potentially attractive therapeutic option to modulate bone remodeling in OA and could become a disease-modifying therapy (3). Meta-analyses studies and clinical trials examining the role of BPs in OA have shown mixed results, possibly due to the heterogeneous patient populations and different

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treatment regimens of BPs used (3). The present review examines the evidence supporting the potential use of the bisphosphonate clodronate in the treatment of osteoarthritis.

Rationale for the use of bisphosphonates in osteoarthritis

The role of the subchondral bone in the pathogenesis of OA was the basis for the rationale for the use of BPs in the treatment of OA (2). BPs are the most important class of antiresorptive drugs commonly used to treat osteoporosis, complex regional pain syndrome (CRPS), bone metastasis, osteogenesis imperfecta and bone Paget's disease. BPs are chemically stable derivates of inorganic pyrophosphate with a very high affinity for bone mineral because they bind to hydroxyapatite crystals. BPs are incorporated into sites of bone remodelling where skeletal turnover is accelerated. Compounds not bound to the skeleton are rapidly cleared from the circulation via renal elimination. The most important characteristics of BPs are the ability to: i) inhibit calcifications, ii) inhibit osteoclasts and macrophages, iii) suppress bone resorption (4).

The most recognized side effects of BPs are i) osteonecrosis of the jaw, which is common during treatment with high intravenous doses of zoledronate or pamidronate for bone metastasis, in patients with poor oral hygiene or in patients with osteomalacia; and ii) atypical femural fracture, a rare side effect, described over the course of prolonged treatment (over 5 years) with oral BPs, due to severe suppression of bone turnover.

BPs can be divided into two groups with different mechanisms of action. Nitrogen containing BPs (alendronate, risedronate, zoledronate, pamidronate, neridronate) are the second generation of BPs. They reduce bone resorption and cause apoptosis of osteoclasts by the blockade of the mevalonate pathway, which induces the accumulation of intermediates able to activate circulating cytokines with consequent inflammatory effects. Non-nitrogen containing BPs (etidronate, clodronate) belong to the first generation of BPs. They are intracellularly metabolized into an analog of ATP (appCCl(2)p), which inhibits mithocondrial oxygen consumption and-differently from amino-BPs- they are recognised to exert anti-inflammatory effects (5).

Anti-inflammatory effects of clodronate

CLO has been shown to be effective in macrophage activation and the reduction of the inflammatory cytokines (IL-1β, IL-6, TNF-α), nitric oxide, cyclooxygenase 2 and prostaglandin E. CLO is also capable of inhibiting matrix metalloproteinases, a class of protease enzymes that are calcium-dependent zinc containing endopeptidases,through its ability to chelate zinc. In a rat model of adjuvant arthritis, CLO was able to reduce the number of swollen joints to the same extent as indomethacin (5). Intra-articular CLO containing liposomes was used in 10 patients affected by rheumatoid arthritis about to undergo knee replacement. CLO was administered 7 days before surgery. After surgery, macrophage depletion and decreased expression of adhesion molecules in the synovia were observed (6).

Analgesic effects of clodronate

CLO can also exert analgesic effects in bone diseases charecterized by edema as CRPS-1 syndrome, avascular osteonecrosis and vertebral fractures.

There are also pre-clinical data showing that intravenous CLO has a peripheral prolonged (up to 14 days) anti-nociceptive activity greater than that observed for acetylsalicilic acid (1). The analgesic effect of CLO in mice was also studied by Shima and colleagues (7). They demonstrated that CLO may enter neurons inhibiting SLC17-mediated transport of glutamate and/or ATP, thereby producing analgesic effects. The Authors concluded that CLO and etidronate may be candidates for a new type of analgesic drug (7). Moreover, CLO is a potent and selective inhibitor of vesicular ATP release, due to its inhibition of purinergic chemical transmission. In vivo, CLO is more effective than other therapeutic agents in attenuating neuropathic and inflammatory pain in mice, without affecting basal nociception (8).

Effect of clodronate in osteoarthritis

CLO is effective in reducing pain with a consequent improvement in functional measures in

erosive osteoarthritis of the hand (EOA) a subset of hand osteoarthritis. EOA may be the sequela of the severe development of non-erosive OA (9). In 2000, twenty-nine patients affected by EOA were successfully treated with intravenous CLO at the daily dose of 300 mg over a course of 7 days every 3 months resulting in a highly significant reduction in pain ($p=0.0001$) and number of tender joints ($p=0.00011$) (9). The dosing schedule was based on our previous experience showing that the efficacy of CLO persists for approximately 3 months. In 2012, twenty-four patients affected by EOA were treated with CLO over a period of 24-months. An initial high dose of intravenous CLO (300 mg/day for 7 days) followed by a maintenance intramuscular dose of 100 mg/day for 14 days every 3 months was administered. The following measures were significantly reduced: pain ($p<0.001$), Dreiser's score ($p=0.012$), number of tender joint ($p=0.011$) with concomitant improvement in strength of right hand ($p=0.04$), strength of left hand ($p=0.016$), physician's global assessment ($p<0.001$), and patient's global assessment ($p=0.021$). We further evaluated the effect of intramuscular CLO in EOA (5). Forty outpatients were divided into two groups: the control group consisted of 16 patients that continued standard treatment with anti-inflammatory or analgesic drugs; the second group consisted of 24 patients, who continued the previous treatment with the addition of intramuscular CLO, administered as follows: 200 mg for ten days (as initial high dose) dose followed after 3 and 6 months by 200 mg for 6 days as mainteinance dose. Our study revealed no significant changes in all parameters in the control group, while in the group treated with CLO consumption of anti-inflammatory or analgesic drugs ($p<0.0001$), pain ($p<0.0001$), number of tender joints ($p=0.0097$), number of swollen joints ($p=0.0251$), Dreiser score ($p=0.019$), and patient's and physician's global assessment of disease activity (both $p<0.001$) were significantly decreased.The functional improvement was also observed by an increase in the strength of the right ($p=0.047$) and left hand (+38%, p=ns). At 6 months, serum COMP (Cartilage Oligomeric Matrix Protein) also significantly decreased ($p<0.0029$) (5). In an earlier study, low-dose intra-articular CLO was shown to be as effective as hyaluronic acid in knee OA (10). CLO is able to induce an anabolic effect on articular chondrocytes, which results in 90% increase in extracellular matrix accumulation (11).

Recently, 23 females, affected by spondyloarthritis were treated with intramuscular CLO 200 mg weekly. CLO was able to upregulate SOX-9 gene, which encodes for the transcription factor responsible for mesenchymal chondrogenic commitment. This result supports the hypothesis of a role of CLO in preventing the degenerative process. CLO also reduced osteoarticular pain and improved mental and physical performance in these patients. In addition, nanoparticle-embedded CLO in an in vitro model of chondrogenic differentiation was also evaluated. This new formulation stimulated SOX-9 expression more efficaciously than CLO alone, suggesting the possibility to use nanoparticle-technology to optimize the efficacy of CLO to counteract the degenerative process (11).

Use of clodronate in painful knee and hip prosthesis

Evidence suggests that the risk of failure of the prosthesis is linked to the patient's pre-existing osteoporosis or osteopenia. In an observational retrospective controlled study with a follow-up period of 8 years it was shown that patients with lower bone mass have a significantly higher risk of failure. The study involved 85 female patients who underwent primary knee replacement, divided into two groups. The first group included 42 patients who had undergone a revision of knee prosthesis for aseptic loosening and the second group included 43 age-matched patients who, in the same year, underwent primary knee replacement without aseptic loosening ensuing. The evaluation of stiffness index with Achilles-QUS system showed that in the first group 20/42 patients (47.6%) had a stiffness index T-score below -2.5, while in the second group osteoporosis was present in 14/43 (32.5%) ($p=0.015$) (12). In addition, an association between BP use and implant survival after total primary arthroplasty of the knee or hip has been documented in two retrospective cohort studies.

The first study included 18,726 cases of total arthroplasty of the knee and 23,269 of the hip.

After five years, the rate of arthroplasty revision was significantly lower (0.93% vs. 1.96%) and the implant survival was significantly longer in 1,912 patients, who were identified as BPs users (13). The second paper included 95,392 patients from the Danish Nationwide Registries with a primary total joint replacement. The risk of revision surgery was lower (-59%) in bisphosphonate users (14). Given that periprosthetic bone loss is the most common complication of arthroplasty, another paper compared oral CLO, administered from 3 weeks pre-surgery until 6 months post-surgery, with placebo, showing significantly less prosthetic migration in the CLO group vs. placebo after 12 months ($p=0.01$). After 5 years, the prosthetic migration was still reduced in the CLO group (-25%). Moreover, intramuscular CLO, administered after surgery, for 12 months at a weekly dose of 100 mg, was able to reduce bone periprosthetic loss ($p<0.05$) in patients treated with total uncemented hip arthroplasty (15).

Clodronate in veterinary practice

There is a growing interest among veterinary practictioners on the use of clodronate, following the publication of a recent randomized double blind placebo controlled study by Frevel et al. in which a single intramuscular CLO dose of 1.4 mg/kg in horses was shown to be effective in reducing clinical signs of navicular disease (16). The latter is a palmar foot degenerative syndrome involving the distal sesamoid bone, with consequent lameless. Due to different clinical conditions leading to lesions of the navicular bone somewhat similar to human OA. 146 horses were divided into two groups. The first group consisted of 111 horses treated with CLO, while the second group consisted of 35 horses treated with placebo. At day 56, using the lameless scale, 75% of the horses in treatment with CLO had an improvement, with only 3% of those in the placebo group. At day 180, a positive trend was still detectable in 65% of the horses in CLO group. Most of them had an improvement by 2 lameless grade (16). Recently Michell et al. studied twelve equestrian team competition horses affected by forelimb lameless (17). In a blind manner six out of them were treated with a single dose of CLO (1.4 mg/kg), while the other six horses were treated with placebo. To detect CTX-I and osteocalcin, blood samples were weekly examinated for 8 weeks before and after CLO administration. As expected, horses treated with CLO had a significant reduction in forelimb lameless ($p=0.01$) but there was no difference in bone turnover markers between placebo or CLO treated horses (17). These findings complement and reinforce those observed in OA patients and provide further insight into other potential mechanisms by which CLO may elicit ots effects.

Potential mechanisms of action of CLO

The peculiar mechanism of action is probably the most important characteristic of CLO, which is the BP with the lowest affinity for bone crystals. Consequently, osteonecrosis of the jaw and atypical femoral fracture are- as expected- very rare during the course of treatment with CLO, even if in Italy (until 2006) intramuscular CLO was the most used drug for osteoporosis, being the pain in the injection site the most common side effect. Consequently, CLO can be used in the treatment of osteoradionecrosis of the jaw caused by radiotherapy for neck cancer to avoid orthodontic tooth movement and may prevent the side effects related to nitrogen containing BPs (7).

OA was for a long time considered as a primary disease of the hyaline cartilage, but in the past two decades the role of subchondral bone has been shown to be crucial. This is the rationale for the choice of BPs in the treatment of OA. CLO has emerged as a promising candidate because of its potent anti-inflammatory and analgesic activity. In humans, CLO has been shown to be effective on pain in knee osteoarthritis (10) and in EOA where it was demonstrated that CLO can reduce serum COMP (5).

COMP is considered to be a reliable biomarker of activity and severity in OA. In particular, in the Johnston County Osteoarthritis Project, 663 patients with hand OA were recruited. Hand symptoms were assessed by Australian-Canadian Hand Osteoarthritis Index (AUS.CAN). Higher AUS. CAN scores were independently associated with higher levels of serum COMP ($p<0.003$).

Moreover, COMP is correlated with the age and severity of synovitis in knee OA, with pre-

radigraphic knee and hip OA and with radiographic progression of knee OA (18).

The role of Transforming Growth Factor β1 (TGF–β1) in the pathogenesis of osteoarthritis has gained attention in recent years. TGF-β 1 is essential for maintenance of articular cartilage metabolic homeostasis and structural integrity has also been found to play an important role in the pathogenesis of OA (19). The association between TGF-β1 and OA severity has also been reported for human hip OA and increased levels of TGF-β1 mRNA and TGF-β3 subtypes have been detected in osteoblasts in subchondral bone from knee OA (20). TGF-β1 has been found to be increased in human OA subchondral bone. The role of TGF-β1 in subchondral bone has also been studied in mice: after anterior cruciate ligament transection TGF-β1 was activated in subchondral bone with evidence of marked changes within 7 days. On the contrary, the inhibition of TGF-β1 has been shown to reduce cartilage degeneration and systemic neutralisation of TGF-β1 relieved the disease in a rodent model of OA.

Finally, CLO in spondyloarthritis patients has been shown to upregulate the SOX-9 gene, encoding for the transcription factor responsible for mesenchymal chondrogenic commitment (11). Nanoparticle-embedded CLO was observed to stimulate SOX-9 expression more effectively than CLO alone, suggesting the possibility to use nanoparticle-technology to optimize the efficacy of CLO to counteract degenerative process.

CONCLUSION

Compared to other rheumatic diseases, there are few treatment options available that can alter the course of OA. BPs have emerged as a potentially attractive therapeutic option to modulate bone remodeling in OA. Findings from recent studies suggest that CLO is not only a symptomatic drug but could also play a role as a disease-modifying drug. Moreover CLO can be useful in the rehabilitation of painful knee or hip prosthesis and generally in painful OA joints without the common side effects normally associated with non-steroideal anti inflammatory drugs.

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