Clodronate: new directions of use

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Summary

Clodronate is the father of bisphosphonates. For over three decades it has been subject of study in biological and clinical areas, proving to be an extremely interesting molecule from different points of view. It has been the first drug for osteoporosis that can be administered pulsatorily (once every 15 days or once a week). This, along with good tolerability, has been the first cause of its success, when there were no solid data in literature about its antifracture efficacy. There are three published studies that prove its antifracture effect: two by McCloskey published in 2004 and 2007 on BMR, and our study about fracture prevention in corticosteroids OP.

In these studies a dose of 800 mg/day orally administered or 100 mg/week i.m. was used, and they are basically the same if you consider that clodronate absorption, orally administered, is on average 1.9%. However, a series of works where higher doses were used (1600 mg orally administered) with greater effectiveness on bone mass, especially in higher risk populations, lead us to consider the use of 200 mg i.m. formulation. First of all, we proved densitometric equivalence of 200 mg i.m./14 days and 100 mg i.m./week in a first study; then, in a second study, we proved a greater densitometric efficacy of 200 mg/week compared to 100 mg/week, clearer at femoral level, where the drug had not proven to prevent femoral fracture because of inadequate bone mass increase at that level. Moreover, as for ibandronate case, monthly dose was doubled compared to pivotal trial, in order to maximize the effects on femoral bone mass and therefore prevent femoral fractures. Consequently, on the basis of the risk envelope, whether it is identified according to BMD and the presence of one risk factor at least or more correctly identified through risk chart (FRAX or DeFRA), you can put forward a differential use of 100 mg i.m. and 200 mg i.m., weekly, “off-label” or every 14 days, adjusting doses in relation to fracture risk and painful symptoms gravity, as well as improving its ease of use and therefore assist compliance. Common experience and clinical and biological works have proved that clodronate has an analgesic effect that can be increased by doubling the doses. The analgesic effect is present not only with patients with fractures, but also with patients suffering from osteoarthritis or arthritis. Therefore, the drug would fit well in the therapeutic program of rheumatic patient, also because of its symptomatic effects. Clodronate at small doses (2 mg) could also have protective effects on cartilage (introduction of intra-articular formulation is expected) and at 10-100 fold higher doses it has certainly anti-inflammatory effects and more specifically antimacrophage and anticytokine effects (IL-1, IL-6, TNFalpha, PGE). These effects are amplified by putting clodronate in monolayer liposomes. This drug, therefore, has to be considered as adjuvant in arthritis therapy, whose origin can be linked to a strong osteoclastic activation caused by an increase of cytokines and the RANKL/OPG relationship. It is clear that clodronate can work on cytokine at first and on osteoclastic effector in the end. The drug has been used “off-label” for decades intravenously in complex regional pain syndrome (CRPS type 1) in relation to schemes that change according to different Authors and according to cumulative doses ranging from 3 to 5 g. The introduction on the market of the 200 mg i.m. formulation could allow to get more practical but equally effective schemes. For example, we used this scheme: 200 mg/day for 10 days and then 200 mg every other day for 20 days (cumulative dose of 4 g in a month). Said scheme can be repeated in the following months in particular cases. Results, as for efficacy and lack of relapses, show that clodronate is the leader drug for this syndrome. In recent years, relationship between costs and benefits has started to matter, especially after the creation of some algorithms, such as FRAX, that let us choose patients with a higher fracture risk in 10 years, and after pharmaceutic-economic models that let us calculate FRAX intervention threshold, on the basis of drug price and monitoring, antifracture efficacy, quality of life and how much a community can or wants to spend. In this respect, a sub-analysis of McCloskey’s study on people over the age of 75, conducted on 3974 subjects, shows that clodronate is more efficient with patients with a higher fracture risk, calculated according to FRAX. Furthermore, another study by McCloskey revealed that, for a 100-pound/year drug (very similar to clodronate), ‘cost effective’ intervention threshold is about 7-10%. In conclusion, clodronate prevents fractures, decreases osteo-articular pain, is easy to handle, tolerable and had a great cost/benefit relationship.

KEY WORDS: bisphosphonates; osteoporosis; fractures; analgesic; anti-inflamatory; bone edema; algodistrophy; periprosthetic loosening.
B. Frediani et al.

Introduction

Clodronate is one of the best known bisphosphonates (Figure 1), in which two lateral chains are made up of two chlorine atoms; it has been largely and effectively used, from the 60s until today, for treating many osteometabolic disorders, generally characterized by excessive resorption: Paget’s disease (1-5), hypercalcemia malignancy (6-8), osteolytic bone metastases (8-10), primary hyperparathyroidism (11, 12). Subsequently new data have appeared in literature about use of clodronate for bone loss prevention and hip replacement stabilization (13, 14) and because of its anti-inflammatory and analgesic actions, for CRPS (15-17), bone marrow edema, osteomyelitis (18, 19), periarthropathy hip pain unresponsive (20), erosive osteoarthritis (21), rheumatoid arthritis (22), painful shoulder (23), osteogenesis imperfecta (24) and transient osteoporosis hip (25). Works by Italian Authors (Filipponi, Giannini, Rossini) from the late 90s have paved the way for using clodronate for prevention of post-menopausal osteoporosis (26-29). As for other bisphosphonates, even for clodronate, for this indication, is planned an oral administration under daily regimen, even though there is still a lack of bridging studies that aim to prove the dose equivalence between oral and parenteral (intramuscular and intravenous) administration. There are studies that show the efficacy of intramuscular administration in post-menopausal bone loss prevention (30, 31) and reduction of fracture risk in glucocorticoid osteoporosis (32).

Clodronate as antiresorptive in osteoporosis

Effects on BMD

The first work leading to an evaluation of clodronate for prevention and treatment of post-menopausal osteoporosis (26-29). As for other bisphosphonates, even for clodronate, for this indication, is planned an oral administration under daily regimen, even though there is still a lack of bridging studies that aim to prove the dose equivalence between oral and parenteral (intramuscular and intravenous) administration. There are studies that show the efficacy of intramuscular administration in post-menopausal bone loss prevention (30, 31) and reduction of fracture risk in glucocorticoid osteoporosis (32).

Figure 1 - Chemical structure of bisphosphonates.

200 mg every 3 weeks with significant increase of BMD and maintenance of positive trend during the study. So the Authors compared clodronate effects on BMD using different methods of administration (continuous- oral or intramuscular or intermitent- intravenous). Continuous administration, both oral and intramuscular, showed best results in terms of bone density increase and same results are obtained with 100 mg/10 days I.M. administration and oral formulation at a dose of 400 mg/day (34). In 2004 a RCT, conducted by McCloskey et al. on women suffering from postmenopausal osteoporosis and other forms of secondary osteoporosis, proved that clodronate at a dose of 800 mg/day orally administered resulted in increases of lumbar and femoral BMD, significantly higher than placebo (35). Furthermore, at the same dose, the medicine proved to reduce loss of femoral bone mass in an old large institutionalized population (more than 5000 people) (36). A further confirmation of the efficacy of 800 mg/day clodronate orally administered on BMD comes from a small RCT lasted three years and conducted by Tanakol et al. on women at postmenopausal age (37). Positive results also emerged from using clodronate intramuscularly. Dominguez et al. tested molecular efficacy in increasing BMD at a dose of 100 mg/week vs once every two weeks. Better results were obtained with the first posology both at lumbar and femoral level, although with both doses significantly higher increases of BMD were obtained, compared to the control group, treated only with calcium and vitamin D (38). In 2003 our working group published a study on the use of 100 mg clodronate one a week, intramuscularly administered on patients suffering from arthritis, about to start a corticosteroid treatment. Bone density evaluations were carried out by dual-energy absorptiometry and heel ultrasonometry at 12, 24, 36 and 48 months from the start of the corticosteroid therapy. The group of patients receiving only additional therapy with calcium and vitamin D faced a decrease in densitometric values (in terms of both BMD and stiffness), while patients treated with clodronate kept bone density values stable. In conclusion, our study proved that clodronate is effective in preventing loss of bone mass in patients suffering from arthritis in corticosteroid therapy (32). Regarding glucocorticoid osteoporosis, there are two other works that tested the efficacy of clodronate treatment in this area, with patients affected by different pathologies, namely inflammatory intestine diseases and asthma, who obviously needed a steroid therapy (39, 40). Furthermore, intramuscular clodronate showed an additive effect on BMD in a cohort of patients with post-menopausal osteoporosis who were taking SERM (Selective Estrogen Receptor Modulators) (41). Favorable results in terms of BMD emerged from an open label study, in which intramuscular clodronate was compared to oral alendronate and risedronate, even on patients aged over 80, for a two-year period (42). The result of the work of del Puente et al. is interesting and it has highlighted the efficacy of intramuscular clodronate in non-responder patients, in terms of BMD, with alendronate treatment (43).

Effects on fragility fractures

Anti-fracture efficacy, main goal of anti-osteoporotic therapies, of oral clodronate shall be demonstrated by McCloskey’s study (35), in which incidence of vertebral fractures at three years was 10.62% for group placebo versus 5.6% for the group treated with clodronate 800mg/day orally administered (equivalent to 100 mg/week I.M.). Further analyses deduced from this study pointed out that clodronate reduced fractures both in post-menopausal osteoporosis and secondary forms and that it...
Clodronate: new directions of use

is effective with patients with or without vertebral fractures at baseline. Subsequently McCloskey's group tested the anti-fracture efficacy of the drug on a large elderly institutionalized population, not selected for osteoporosis. In three years of study, out of 5592 women, 56 of clodronate group and 58 of placebo group faced femoral fracture; however, considering every kind of fragility fracture, clodronate treatment reduced fracture incidence of 20% compared to placebo (36). Anti-fracture efficacy of intramuscular formulation is less documented; key data come again from our study on patients affected by arthritis in steroid therapy; relative risk for every type of fracture in treated group compared to placebo (calcium and vitamin D) was 0.63 and relative risk for multiple vertebral fractures was 0.25 (32).

Unfortunately, in this field there is a clear lack of bridging studies, that allow us to pick out data on the anti-fracture efficacy of oral formulation and applying them on the intramuscular one, therefore using data on BMD and bone markers as surrogate end-points, which actually are.

Recently, a systematic review and meta-analysis of literature about anti-fracture efficacy of clodronate in patients suffering from osteoporosis or neoplastic diseases has been published (44). Research pointed out 18 trials, including 13 on patients affected by malignancies, 4 on patients with osteoporosis and 1 on women of an advanced age, committed to healthcare institutions; 13 trials included a control arm with placebo. Duration of the treatment period and the follow-up was between 3 months and 5 years. Meta-analysis proved that the clodronate treatment was associated with a decrease of chances of new fractures, compared to controls (OR=0.572, 95% CI 0.465-0.704 for new vertebral fractures; OR=0.668, 95% CI 0.494-0.905 for new non-vertebral fractures; and OR=0.744, 95% CI 0.635-0.873 for all types of new fractures in all works in which vertebral and non-vertebral fractures were not separately considered). Overlapping results were obtained in a separated analysis of neoplastic and osteoporotic patients. The result of meta-analysis has showed that clodronate treatment is effective at decreasing vertebral, non-vertebral fracture risk and every other kind of fracture as well, in patients with skeletal fragility.

Formulations and dosages as antiresorptive and anti-fracture

Clodronate is available as tablets of 400 mg per os and as preparation for intravenous infusion 300 mg/10 ml to be diluted with 5% saline or glucose solution. Only in Italy it is sold also in the form of ampoules of 100 mg and 200 mg to administer intramuscularly for the prevention and treatment of post-menopausal osteoporosis. After the release in circulation, the drug is bound for 36% to plasma proteins, whereas 20-25% is picked up from the bone. It does not undergo metabolic processes and the majority is excreted intact with urines; renal clearance is 6-7 l/h. As all bisphosphonates, clodronate has a very low bioavailability equal to 1.9%, when orally administered; therefore one tablet of 800 mg corresponds to an absorbed dose of 15 mg of the drug, equivalent to 105 mg/week (45). Absorption, however, is decreased by simultaneous assumption of food and drink, in particular if containing calcium or iron (61). Furthermore, according to the requirements imposed by the American FDA about bioequivalence, there could be a variability in the bioavailability of the active substance between general products and brands equal to 25%. Clodronate for intravenous infusion is used especially for (the) short-term treatment in patients with hypercalcaemia of malignancy; however, intermittent intravenous administrations have been used in clinical trials for the treatment of post-menopausal osteoporosis (33, 34). Intramuscular formulation has pharmacokinetic properties fully superimposable to intravenous formulation, but contrary to the latter and its intermittent use, has been designed for a continuous use. A pharmacokinetic comparative study, between the intravenous and intramuscular 200 mg formulations, conducted on 20 healthy volunteers pointed out that the drug peak concentration is 16.1 mg/l i.v. and 12.8% I.M.

half-life is the same of 6.31 hours; clearance is nearly overlapping, equal to 4.99 l/h intravenously and 4.47 I.M. and the percentage of total dose excreted with urines after 48 hours is 84.1% for I.V. and 82.5% for I.M. (46). Since the drug is eliminated by the kidney, a dose adjustment is planned in patients affected by kidney failure; for a creatinine clearance between 50-80 mL/min it is recommended to use 75-100% compared to the normal dose; for a creatinine clearance between 12-49 mL/min it is recommended to use 50-75% compared to the normal dose; lastly, for an important kidney failure with a creatinine clearance <12 mL/min it is recommended to use 50% of the normal dose (47).

As already reminded, no comparative study has ever been conducted to compare the effect on bone mass of 800 mg administration per os and 100 mg I.M./week, even though in many studies evaluating clodronate effect on bone density, BMD increase was similar in the two methods of administration (29, 35). In 1999 Rossini proved that the 100 mg I.M./week administration was more effective on BMD compared to the same dose administered every 15 days (29). It is not surprising, since a direct relationship between bisphosphonate dose and effect on BMD has been emphasized many times (48). Interval prolongation of administration, within limits determined by bisphosphonate affinity, requires an equally proportioned increase of the dose, in order to maintain an equal densitometric efficacy. Consequently it could be expected that 100 mg/week can determine equal effects of 200 mg every two weeks, in terms of bone density. In the case of clodronate, less similar than other bisphosphonates, the interval prolongation of administration and its increase of dose has a limit, as already proven by Filipponi (34), which is more or less 15-20 days. Even for an amino-bisphosphonate such as ibandronate, tested as antifracture at daily dose of 2.5 mg orally administered, the proposed dose for the monthly administration has been doubled (150 mg) compared to the 75 mg dose predicted by a simple mathematical calculation (2.5 mg/day x 30 days). This has two justifications: the first one is that, in terms of BMD increase at least, the interval prolongation of administration involves a loss of efficacy, even if it is about broadly equivalent dosages; and it is not hard to understand, considering that the duration of osteoclast activation in units of remodeling is of 15-20 days and that the units of remodeling are not synchronized with each other (49). The second reason of the doubling of the predicted monthly dose consists in the necessity for ibandronate of enhancing the effect on femoral bone mass, used as substitute for the anti-fracture effect; ibandronate did not show anti-fracture efficacy at non-vertebral and femoral level at the dose of 2.5 mg/day (50-52). Also for clodronate, some studies with patients at a high risk of secondary osteoporosis (heart-transplanted patients, taking cortisone patients, patients wearing prosthesis), who had BMD evaluation as end point, proved that doses higher than 800 mg (1600 or 2400 mg) comported higher
BMD increases (53, 54). In the light of these considerations we did a work at our Institute to test the effects on BMD of clodronate, administered at the dose of 200 mg/week compared to the dose in use of 100 mg/week (55). The study has been conducted on 90 women with osteoporosis and more than 1/3 showed vertebral collapses at basal. Assignment to the two treatment groups was casual and every patient received the following supplementation: an initial bolus of 300 000 UI of vitamin D and a daily dose of calcium 1g + vitamin D 880 UI. By doubling the dose of clodronate given weekly were obtained increments of BMD higher and more rapid bone mass in the spine but especially in proportion to the femoral level. In fact, the increase in BMD at 24 months becomes significant compared to the 12 months both at vertebral level that femoral (Figure 2). Substantially the increases registered in the first year at double dosage are comparable (and even higher in some cases) to those registered after two years of therapy with an inferior dose. This is in the line with the results obtained with alendronate or ibandronate at different dosages (48, 50, 52), confirming that even for clodronate a margin of greater effectiveness exists with a further dose increase compared to previous studies. Increases of bone mass with clodronate 200 mg/week, “off-label” are similar to those obtained with 10 mg/day and 70 mg/week of alendronate (56), 150 mg/month of ibandronate (50,52), 5 mg/year of zoledronate (57) and 25 mg/month of neridronate (58), that are notoriously the bisphosphonates with best effects on BMD. All that has been confirmed, even in the absence of size statistically adequate, by the trend of incidence fractures, that were less than half in the group at a double dose than the group at a lower dose. Furthermore, we recently published a randomized, open label parallel-group study, in which were analyzed the effects of clodronate 100 mg/week, compared to 200 mg every two weeks on bone mass in a population of 60 women, aged between 50 and 80, affected by postmenopausal osteoporosis (59). The study lasted two years and proved that lumbar BMD increase, compared to basal, was significant for both treatment groups, both after one and two years. Femoral neck BMD increased in both groups; it reached statistical significance for 100 mg already at the first year, compared to basal, for the group treated with 200 mg every two weeks, the increase reached statistical significance only at the second year; increase of the entire femur BMD was significant just for 100 mg group at the second year (Figure 3). Definitely our work highlighted an almost equivalent effect on BMD by the two different administration schedules of intramuscular clodronate. Also in terms of tolerability and safety, the two schemes did not show any differences: a mild pain in the injection site has been reported by three patients, one of 100 mg group and two in 200 mg group. A further confirmation of biweekly administration of clodronate comes from Muratore et al. study (60), in which the two regimens of administration were compared (100 mg/week and 200 mg biweekly) in terms of lumbar and femoral BMD, bone turnover markers, safety, tolerability and painful symptoms (VAS - visual analogic scale - of the patient) and adherence. A total of 60 women suffering from postmenopausal osteoporosis were randomized in two treatment groups and were
followed for 12 months, and at the end of that period patients of both groups have showed lumbar and femoral BMD increase, resorption markers decrease and pain reduction practically similar, without statistically significant differences. Also in this study, just like the previous one, the only side effect was a mild pain in the injection site. The most interesting result, however, involves adherence: six patients of the group treated with weekly schedule stopped taking the drug; on the contrary, no patient of the group treated with the biweekly schedule interrupted the therapy. Definitely this work confirmed efficacy and safety of biweekly regimen, in the same way as the weekly administration, with the benefit that injections more spread over time lead to an increase of the patient’s persistence. This aspect is anything but minor, considering that literature about bisphosphonates clearly indicates how persistence (continuation of treatment for the entire prescribed duration) and compliance (commitment to the treatment indications) and ultimately adherence (combination of persistence and compliance) are often inadequate in the long-term treatment, with suboptimal clinical result and reduction of the cost-benefit relationship (61-63). In this respect a treatment indications more spread over time lead to an increase of the patient’s persistence. This aspect is anything but minor, considering that literature about bisphosphonates clearly indicates how persistence (continuation of treatment for the entire prescribed duration) and compliance (commitment to the treatment indications) and ultimately adherence (combination of persistence and compliance) are often inadequate in the long-term treatment, with suboptimal clinical result and reduction of the cost-benefit relationship (61-63). In this respect a study on the bisphosphonate use conducted on more than 35000 women (source: insurance database in the USA) followed for 2 years, proved that those with compliance lower than 50% did not benefit much from the treatment, while positive effect of the therapy showed only when compliance exceeded the threshold value of 50% (64). It is sure that a prescription that does not generate clinical benefits means a waste of resources, in financial terms as well, for healthcare system and individuals themselves, who bear the drug cost; it is doctors’ duty to consider even the aspects about therapy adherence when managing patients, always bearing in mind that the first and essential step is to communicate clearly and effectively.

200 mg clodronate: indications and regimens as anti-fracture in primary and secondary prevention

Once the efficacy of clodronate 200 mg i.m. is proven, we have to rationalize its use, keeping in mind the save of number of injections compared to the 100 mg at the same cumulative dose, or if we want to, the possibility of reaching a higher cumulative dose at an equal number of intramuscular injections. Introduction of fracture risk cards put the long-standing matter of which is the fracture risk threshold at ten years to which match the therapeutic intervention threshold. Use of pharmaceutical-economic models, borrowed from cardiovascular framework, suggests that the intervention threshold cannot be the same for every anti-osteoporotic drug, but that has to be determined for every single drug on the basis of cost/benefit relationship. Another nullifying factor concerns the possibility of expenditure by our Institutions for the matter of fracture prevention. This way, population groups will be determined and they will have a certain fracture risk at ten years above which the pharmacological intervention will be cost-effective. Pharmaceutical-economic studies on a large scale, about osteoporosis, were conducted by Kanis’s group (65) on the anglo-saxon reality and tell us that the fracture risk threshold at ten years is 10% to make the use of clodronate 100 mg/week (or alternatively 200 mg/2 weeks) cost-effective is 10% at ten years; however, if it were to consider 200 mg/week in “off-label” would be the threshold of 15%. The intervention threshold so determined is independent of age, contrary to what happens here with the application of note 79, where we have a threshold that changes from 10% of risk at the age of 50 to 40% of risk at the age of 80. In this way, use of clodronate allows the treatment for many patients from the age of 55 excluded from note 79.

Is it possible to transpose into clinical practice these complex pharmaceutical-economic considerations?

The answer is of course positive, just take a step back on the evaluation of fracture risk and transform in an analytical way the threshold value of 10% into number of risk factors that produced it, so that it is possible to evaluate cost/effectiveness relationship of prescription, even with the impossibility of using a fracture risk algorithm. Risk cards must be used; they relate BMD to number and weight of factor risks. We can draft a chart (Table 1) with factor risks and their weight in terms of risk unit (one unit corresponds to a relative risk of 2). This way we see that for clodronate 100 mg/week or 200 mg/2 weeks the intervention threshold corresponds to 3 factors of average risk weight or 2 of average weight and 1 of high weight. However, if for the same drug, clodronate, we double the dose, meaning 200 mg/week, the intervention threshold goes from 4 to 6.

In brief, we could propose to divide patients in 3 groups, on the basis of fracture risk calculated with algorithms or on the...
basis of BMD and risk factors, for which we suggest use of differentiated therapeutic interventions (Table 2):

1 group: so, after 60 years of age, clodronate 200 mg/month or 100 mg every 2 weeks can be used, in the limits of cost-effective relationship, with subjects at the lowest risk (between 5 and 10%), basically in osteopenic and without additional risk factors;

2 group: clodronate 200 mg every 14 days or 100 mg/week (dosages where it is registered) can be used in patients with a fracture risk between 10 and 20%, basically osteoporotic or osteopenic with one additional risk factor;

3 group: clodronate 200 mg/week, “off-label”, is reserved for subjects with the highest fracture risk (>20%), i.e. serious osteoporotic with fractures, osteopenic with fracture or at least 2 additional risk factors.

Clodronate anti-fracture efficacy in patients at different risk, including osteopenic, was proved by McCloskey’s work, in which 5600 normal, osteopenic and osteoporotic patients with different risk factors were involved. In any case, clodronate anti-fracture efficacy was independent from BMD basal level and increased with increasing of other risk factors.

Clodronate as anti-inflammatory and pain-relieving drug*

Clodronate, compared to other bisphosphonates, has interesting anti-inflammatory properties and an effect on pain that, with a good safety profile, have made it a widely used drug over the decades, despite the introduction of new and powerful molecules. Amino-bisphosphonates, because of their mechanism of action (Figure 4), can cause the well-known acute phase reactions (APS), especially if intravenously administered. Block of the mevalonate way causes accumulation of intermediate metabolites that activate circulating lymphoid cells Ty/δ, with massive release of pro-inflammatory cytokine, including TNF-α, INF-γ, IL-6, that trigger flu-like syndrome, typical of APS (66). This kind of reaction does not happen with nitrogen-free bisphosphonates (Figure 5) that act differently, not interfering with mevalonate metabolites; furthermore, clodronate might have an inhibitory effect on the release of inflammatory cytokines (IL-1β, IL-6, TNF-α) and COX-2 (cyclooxygenase 2), that underpins prostaglandin E2 production, key mediator of inflammation (67) (Figure 6). Interesting applications of bisphosphonates are those on animal models of collagen-induced arthrosis, where rational use of the anti-erosive drug is ascribed to an important current of the most recent scientific literature, where the role of osteoclastic activation by pro-inflammatory cytokines in the genesis of structural bone damage and erosions is emphasized. Inhibition of bone resorption, from this point of view, is a key point in arthrosis therapy. However, in animal models, the use of amino-bisphosphonates caused exacerbation of joint phlogosis, even though it showed a positive effect on structural bone damage (68), whereas use of clodronate had positive effects both on inhibition of structural damage and joint phlogosis (69, 70). Bonabello’s works, and more recently Kim’s, on animal models (74, 75, 85) highlighted a pain-relieving and anti-nociceptive effect of clodronate both at central and peripheral level independent from anti-fracture effect. There are many suggestions coming from reports of different authors that point out pain-relieving properties of the molecule, in different fields of use (20-23, 73-78). Clodronate analgesic effect is known and pain-relieving properties of the molecule, in different fields of use (20-23, 73-78).

Clodronate anti-fracture efficacy was independent from BMD basal level and increased with increasing of other risk factors.

Table 1 - Cost/effective intervention threshold in osteoporosis on the basis of the number of units of risk (WTP: 30000 €).

| Osteopenia pathology | 1 |
|----------------------|---|
| Familiarity for fractures | 1 |
| BMD ≤ -2.5 | 1 |
| BMD ≤ -2.5 | 2 |
| BMD > -2.5 | 3 |
| 1 Fracture | 1 |
| 2 or more fractures | 2 |
| Vertebral Fracture < 40% | 2 |
| Prednisone dosage ≤ 5 mg | 1 |
| Prednisone dosage > 5 mg to 15 mg | 2 |
| Prednisone dosage > 15 mg | 3 |
| Previous falls in the last year | 1 |
| Age ≥ 65 years and < 80 years | 1 |
| Age ≥ 80 years | 2 |
| Smoking | 1 |
| Alcohol 3 units | 1 |
| TOTAL | x |

Table 2 - Treatment regimens with clodronate recommended.

| T-score | TRAX |
|---------|------|
| Osteopenia (-1 < -2.5) or Normality with 1 fracture risk | ≥ 5 and < 10 |
| 200 mg/month | 100 mg/14 days |
| Osteoporosis or Osteopenia with 1 factor risk | ≥ 10 and < 20 |
| 200 mg/14 days | 100 mg/week |
| Fractures or Cortisone | ≥ 20 |
| Osteoporosis with ≥ 2 factors risk | Osteoporosis with ≥ 1 factor risk |
| Osteoporosis with pain | * |
| 200 mg/week** | 100 mg twice a week |

* Antalgic therapy can have 1-2 g. of Clodronate in 5-10 days.
** Such uses of clodronate are “off-label”.

Formulations and dosage regimens as anti-inflammatory and analgesic*

On the basis of the described rational use, clodronate has been used for many years for treating numerous osteo-articular diseases, different than those under indications. That happens thanks to its anti-inflammatory and analgesic properties that are autonomously associated with bone effect. In these cases, experience and clinical practice guide choices on dosage regimens, that can be based on works (some RCTs, case reports and case series) found in literature. So we see that in 2000 Sinigaglia and Varenna’s group conducted a study that proved clodronate efficacy in CRP syndrome at a dose of 300 mg/day intravenously for 10 consecutive days (Table 3) with important variations of VAS and CGA (Figure 8) (17). The proposal of Saviola et al. is interesting, using clo-

Table 2 - Treatment regimens with clodronate recommended.
dronate in the treatment of hand erosive osteoarthritis (83), rheumatic disease that does not have a specific treatment and it is still a challenge for clinicians. Protocol planned that a group of patients was treated for 24 months with clodronate 300 mg intravenously for 7 days, followed by clodronate 100 mg I.M. for 14 days every 3 months; a second group of patients was treated with hydroxychloroquine 400 mg/day for 30 days, followed by 200 mg/day for the following 11 months. All the evaluated items (function, pain, disability) showed that clodronate could be an effective therapy hand erosive osteoarthritis, contrary to hydroxychloroquine. A very recent RCT attests symptomatic effectiveness of clodronate, intra-articular administered at a dose of 2 mg/week for 4 weeks versus saline solution (87); the same workgroup published a work about dose-ranging and comparison of intra-articular clodronate versus hyaluronic acid, proving non-inferiority of clodronate, compared to the latter (88). There is an interesting case-report that describes ankle algodystrophy in a patient affected by psoriatic arthritis successfully treated with clodronate 100 mg I.M. with the following scheme: “one injection a day, every day for the first week, one injection every other day for the second week, one injection every 3 days for the third week and one every 4 days for the fourth week, then one ampoule weekly for the following two months” (89). In the light of the new formulation of clodronate 200 mg I.M., it is possible to propose many practical therapeutic schemes in numerous bone and joint disorders and in particular in algodystrophic syndrome, in relation to anti-inflammatory and analgesic properties that, with same injections, allow to reach an adequate cumulative dose (Table 4).

Clodronate and periprosthetic loosening

Scientific progress in medical and technological fields over the last few decades led to a progressive improvement of results of orthopedic surgery of prosthetic replacement, in particular hip arthroplasty and knee replacement. Results that are often affected by the familiar problem of aseptic movement of prosthetic segment; to overcome this problem, in addition to more sophisticated surgical techniques, surgeons make use of materials that, combined, minimized friction and wear particles formation, whose accumulation plays a key role in the aseptic loosening of the prosthesis. Loosening of prosthetic components is, indeed, the most frequent cause of surgery failure and it is the first indication to revision surgeries. The success of an orthopedic surgery is the optimal setting of artificial components to biological substrate (90).
To understand rational use of clodronate in prevention and treatment of periprosthetic osteolysis we need to keep in mind the biological mechanism at its base. Generally, materials used for the construction of articular prosthetics are inert towards the human body and are tested, through many accurate biocompatibility tests, to evaluate biological reactivity of cells and tissues toward themselves. The problem of foreign object reaction is not, therefore, linked to toxicity (91). The main point is phagocytosis, done by macrophages, that include cells, substances and corpuscles in their cytoplasm not recognized as constituents of the same organism. The goal is the enzymatic degradation of foreign material; in the case of wear particles produced by prostheses, they cannot be degraded or reduced to simpler units by macrophage enzymes, therefore they activate an enzymatic production that is self-sustaining and grows larger in time, producing necrosis for autolysis of the cells responsible for phagocytosis. Release of lysosomal enzymes in the pericellular environment leads to a modification of tissues affected by the phenomenon (92, 93): in the case of bone tissue, bone matrix resorption happens, therefore the term 'osteolysis', commonly used to described the most common radiological aspects of loosening of articular

Table 3 - Treatment regimen of algodystrophic syndrome with clodronate 300 mg intravenously administered (Varenna) (17).

| CLODRONATE 300 mg /day | for 10 days | = 3 g |
|-------------------------|------------|------|
| Total                   | 10 days    | = 3 g |

Figure 7 - Vertebral fractures and pain. Study in 30 patients with fragility vertebral fracture and with acute vertebral pain, diagnosed 1-5 days earlier than usual. They were treated with clodronate 300 mg i.v. according to the following regimen: 5 slow infusions/week for 4 weeks (total: 6 g) or paracetamol 3 g/day. Using clodronate 200 mg i.m., you could get in 1-2 months the same result keeping the same cumulative dose (6 g) (81).

Figure 8 - Algodystrophic syndrome. Variations of visual analogic scale (VAS 0-100) and of clinical global evaluation (CGA 0-3) at basal level and after Clodronate therapy for 10 consecutive days (Varenna et al, 17).
prostheses. It needs to be kept in mind that macrophage ability of incorporating the particle within lysosomes to try enzymatic degradation is conditioned by the size of the particle itself: if it exceeds the macrophage dimensions, it will be included in the cytoplasm of a giant cell, but still in extra-lysosomal position. If its dimensions are even bigger, it will be encapsulated in a fibrous membrane that generally includes giant cells. In both cases there is not any stimulation of enzymatic production. Only small particles and compatible for lysosomal inclusion activate the osteolytic process (Figure 9).

This mechanism is at the basis of the majority of aseptic loosening and it must not be adsorbed by a classical inflammatory process: in fact, the study of periprosthetic tissues after aseptic loosening revision highlights an extended proliferation of macrophages, that swallowed wear particles and infiltrate periprosthetic tissues, but not the typical inflammatory cells, meaning polymorphonuclear neutrophils and lymphocytes. When local accumulations of lymphocytes or infiltrated purulent fronds are occasionally observed, one rather suspects a superimposed bacterial infection, event at high risk in accumulations of granulation tissue from foreign object (94). As we have already seen for clodronate anti-inflammatory effects (Figure 6), among the most interesting and peculiar mechanisms of action of this nitrogen-free bisphosphonates we have to name its inhibition on the release of phlogogenic mediators and nitric oxid by activated macrophages (95). Right in this peculiarity we find its rational use in periprosthetic osteolysis, without forgetting its analgesic effect, that is certainly helpful when managing patients, as pain is a building block of the matter (we must consider that these patients get to prosthesis because of pain and functional impotence and they face the same issues after surgery, however with different pathogenesis). After numerous animal and in vitro studies dating from the 90s that showed how bisphosphonates were able to inhibit bone resorption in the presence of principal biomechanical conditions that lead to prosthetic loosening, one recent work moved on to clinical human studies. In particular, literature reviews allow us to point out some interesting works that test clodronate use in this field.

In 2002 Massari’s work evaluated 21 subjects under hip replacement cementless surgery in osteoarthritis treated with clodronate 100 mg/day I.M. from the 7th post-surgery day for 7 days, then 100 mg/week for 6 months and 100 mg/14 days up to 12 months after surgery; they were compared to a control group of 24 patients of a prospective study for periprosthetic densitometric evaluation. Femoral periprosthetic BMD showed how bisphosphonates were able to inhibit bone resorption in the presence of principal biomechanical conditions that lead to prosthetic loosening, without forgetting its analgesic effect (adapted by Denis Nam et al. Clin Orthop Relat Res. 2013) (98).

Over the last 20 years, clodronate proved its anti-fracture efficacy linked to analgesic effect and such effects can be optimized by picking the patient according to clinical risk. Use of different doses and administration intervals make clodronate the best handling anti-osteoporotic drug on the market.

The introduction of 200 mg formulation further improves this handy characteristic, making it possible to get the same effectiveness of 100 mg/week formulation, with half the injections (200 mg/14 days) and better treatment adherence. However, it is possible to improve therapeutic and analgesic effectiveness of clodronate by doubling the dose and keeping the same number of injections of 100 mg/week i.e. 200 mg/week.

In pain management of varying degrees, the great drug handling of the drug and in particular the introduction of 200-mg formulation is even more important, as it makes it possible to rapidly adjust and personalize the various therapeutic schemes in different osteo-articular diseases, on the basis of patient’s the clinical evaluation.

Table 4 - Treatment regimen of algodystrophic syndrome with clodronate 200 mg i.m. (Frediani).

| Treatment          | Frequency | Duration | Total |
|--------------------|-----------|----------|-------|
| CLODRONATE 200 mg | every 2   days | for 20 days | 2 g   |
|                   |           |          |       |
| CLODRONATE 200 mg | every 2   days | for 20 days | 2 g   |
| Total*            |           | 30 days  | 4 g   |

* possibly to be repeated

Conclusions

The possible uses of clodronate included in the previous three paragraphs are "off-label". 

Use of different doses and administration intervals make clodronate the best handling anti-osteoporotic drug on the market.

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Figura 10 - Periprosthetic Loosening. Randomized double-blind study with radiostereometric evaluation in 50 patients with gonarthrosis subjected to total limb prostheses surgery (NexGen) and treated with: clodronate 1.6 g /day per os or placebo with the following dosing schedule: 3 weeks before surgery and up to 6 months in post-operative [using 200 mg i.m this is the dosing schedule: 200 mg/week for 3 weeks before surgery and up to 200 mg/week for to 6 months in post-operative]. (Hilding M, Aspenberg P. Postoperative Clodronate decreases prosthetic migration: 4-years follow-up of a randomized radiostereometric study of 50 total knee patients. Acta Orthop. 2006 Dec; 77(6):912-6).
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