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ORIGINAL ARTICLE

# Intramuscular clodronate in erosive osteoarthritis of the hand is effective on pain and reduces serum COMP: a randomized pilot trial—The ER.O.D.E. study (ERosive Osteoarthritis and Disodium-clodronate Evaluation)

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**Abstract** We evaluated the efficacy and safety of intramuscular clodronate (CLO) for the treatment of active erosive osteoarthritis of the hand (EOA). Forty outpatients treated with anti-inflammatory (NSAIDs) or analgesic drugs since at least 6 months, for at least 3 days a week, were randomly divided into two groups. Group A: 24 patients treated for 6 months with intramuscular (i.m.) CLO added to usual NSAIDs or analgesic drugs. The attack dose was 200 mg/day i.m. for 10 days followed by a maintenance dose of CLO i.m. 200 mg/day for 6 days after 3 and 6 months. Group B: 16 patients who continued the usual treatment with anti-inflammatory or analgesic drugs. Patients in both groups reported in a diary, day by day, the consumption of symptomatic drugs. In group A, the 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 ($p = 0.0119$), and patient's and physician's global assessment of disease activity significantly decreased (both $p < 0.001$). At 6 months, serum COMP also significantly decreased ($p < 0.0029$). Strength of right ($p = 0.0465$) and left hand (+38%, $p$ = ns) significantly increased. In group B, there was no significant change in all parameters considered. Intramuscular CLO in EOA of the hand is effective and safe on pain with a significant reduction in the consumption of anti-inflammatory or analgesic drugs, increasing the functionality of the hands. Serum COMP reduction suggests that CLO could play a role as a disease-modifying drug (EudraCT number 2013–000832-85).

**Keywords** Bisphosphonates · Cartilage oligomeric matrix protein · Clodronate · Comp · Erosive osteoarthritis of the hand

## Introduction

The role of inflammation has been recently advanced as pivotal in osteoarthritis onset and progression [1]. The involvement of bone in osteoarthritis has been considered to be secondary to cartilage damage as expression of an adaptation of the joint. Recent clinical studies with magnetic resonance imaging (MRI) demonstrated that bone alterations could be observed in early stages of the disease, even before cartilage lesions. Moreover, there is a strong evidence of an association between subchondral bone mineral density and osteoarthritis [2, 3].

Erosive osteoarthritis (EOA) of the hand is a subset of hand osteoarthritis defined radiographically. Two or more erosions in the distal interphalangeal joints (DIPs) or the proximal interphalangeal joints (PIPs) are necessary to confirm the diagnosis [4]. Compared to non-erosive osteoarthritis, more severe and frequent synovitis is detectable by Doppler ultrasonography. Synovitis is associated with the development of new bone erosions [5]. The typical clinical pattern of the disease is characterized by the presence of inflammatory flares of the interphalangeal joints with severe pain, erythema, and swollen joints with secondary deformations or subluxations. It is still under debate if EOA is a separate entity or a phase of the normal process of the hand osteoarthritis [6, 7]. The differences between EOA and non-erosive OA of the hand are evident. However, EOA may be the sequelae of the severe development of non-erosive OA [8].

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In the Venetian area, about 8.5% of patients over 40 years and affected by OA of the hands suffer from EOA [9]. Up to date, no guidelines on the best therapeutic approach for EOA are available. The most commonly used therapies include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Both drugs are frequently inadequate, especially in the course of an inflammatory flare. Intra-articular injections of glucocorticoids (GCs) are more effective, but there is no evidence that they are able to reduce erosion progression [10]. Slow-acting symptomatic drugs for OA (SYSADOA) are generally considered to be of limited efficacy in real life [11, 12]. Hydroxychloroquine was used in two small cohort studies but the real efficacy of the drug is still under debate [13–15]. More recently, adalimumab significantly counteract the progression of joint damage, whereas some cases were successfully treated with anakinra and with intra-articular infliximab [16–18].

In a first retrospective paper in 2000, intravenous clodronate (CLO) was effective to treat painful episodes [19]. More recently, a second paper showed that CLO was able to reduce pain and disability, while the hand strength improved [15].

CLO is a first-generation, non-nitrogen-containing bisphosphonate (BP) with a peculiar mechanism of action [20, 21]. The drug is available in tablets and ampoules for intramuscular (i.m.) and i.v. injections, currently registered in Europe for the treatment of postmenopausal osteoporosis.

Cartilage oligomeric matrix protein (COMP), also known as thrombospondin 5, is considered as a biomarker of osteoarthritis. It is a homopentameric non-collagenic, extracellular matrix glycoprotein member of the thrombospondin family of calcium-binding proteins [22]. It is mainly expressed in cartilage but also in other tissues, and its function is to bind type I and type II collagen fibers and to catalyze fibrillar collagen assembly [23].

In this study we report the results of a randomized trial in which active painful EOA was treated with intramuscular CLO for 6 months. The primary endpoint of the study was the evaluation of the clinical efficacy and safety of intramuscular CLO at the dose of 200 mg in the treatment of EOA of the hand. The secondary endpoint of the paper was the evaluation of the efficacy of the drug through the measure of the use of anti-inflammatory or analgesic drugs and the changes of serum COMP.

## Methods

### Patients

The study was carried out on outpatients referred to the Rheumatology and Rehabilitation Unit of the Maugeri Clinical Scientific Institute IRCCS in Castel Goffredo, Mantua, and to the Department of Medicine, University of Verona, Italy, between December 2013 and July 2016.

The protocol was approved by the local Review Board and by an independent ethics committee (Comitato Etico Centrale della Fondazione Salvatore Maugeri, Pavia, Italy) (EudraCT number 2013-000832-85). All the enrolled patients gave their written informed consent to participate, obtained according to the Declaration of Helsinki.

Inclusion criteria were as follows: male and female aged over 18 years, affected by EOA of the hand, diagnosed according to radiographic criteria (sharp marginal defects, central crumbling erosions, gull-wing or saw-tooth deformities), and treated with NSAIDs or analgesic drugs since at least 6 months, for at least 3 days/week; with pain score ≥4/10 evaluated with a visual analog scale (pain-VAS); two or more PIPs or DIPs involved; and treatment with glucocorticoids (GCs) including infiltrations, DMARDs, or SYSADOA stopped at least 3 months before the beginning of the study. Rheumatoid factor (RF), antinuclear antibodies (ANA), and anticyclic citrullinated peptide antibodies (anti-CCP) blood/serum values had to be negative.

Exclusion criteria were as follows: inactive EOA; EOA with functionally irreversible damages (ankylosis); renal, cardiovascular, neurologic, psychiatric, and neoplastic diseases; rheumatic disease other than EOA; carpal tunnel syndrome; alcoholics, addicts; and pregnancy or breastfeeding.

### Study design

This study is a randomized, single blind pilot study. To preserve blinding, evaluation of patient outcome was performed by a physician blinded to the treatment.

The study was planned as a pilot parallel group design study to enroll 40 outpatients. Participants were randomized in two groups with a list generated by a person not involved in the study through PROC PLAN of the SAS Software System according to a completely randomized design balanced for center.

Patients in group A, in addition to their usual analgesic or anti-inflammatory therapy, were treated with intramuscular CLO (Clasteon®, Abiogen Pharma, Pisa, Italy) at the daily dose of 200 mg for 10 days, followed after 90 and 180 days by i.m. CLO at the daily dose of 200 mg for 6 days. This schedule was chosen on the basis of previous experience [15] where the intravenous attack dose was of 2.1 g and the maintenance dose was of 1.4 g, every 3 months.

Patients in group B continued their previous treatment with NSAIDs or analgesic drugs.

All patients of both groups had to register on a diary, day by day, the consumption of symptomatic drugs.

During the whole study period, no intra-articular infiltrations and no substitution of NSAIDs was performed.

All patients were evaluated at baseline and during a planned ambulatory visit at months 1, 3, and 6 after the onset of the treatment. The following parameters were monitored: number of swollen joints; number of tender joints; number of deformed joints; hand disability index calculated by means of Dreiser's questionnaire, in the Italian version proposed by the Gruppo Italiano Artrosi [24, 25]; pain measured by means of a 10-cm-long horizontal visual analog scale (pain-VAS); strength (expressed in bar) measured in both hands by the mean of three tests with a special air dynamometer (Dynatest, Rudolf Riester GmbH Co, Jungingen, Germany); morning stiffness in minutes; global self-assessment of disease activity expressed separately by the physician and patient using a VAS scale (10-cm-long horizontal visual analogical scale); and the consumption of the usual anti-inflammatory of analgesic drugs. Moreover, at baseline and at months 1, 3, and 6, all patients underwent blood tests to determine the following serum parameters: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (normal value/0.5 mg/dl), alkaline phosphatase, creatinine, calcium. The Serum Cartilage Oligomeric Matrix Protein (COMP) was tested at the baseline and at month 6.

The Consolidated Standards of Reporting Trials (CONSORT) recommendations were followed in reporting results of this trial.

### Sample collection and storage

Blood samples were withdrawn using standard venipuncture technique between 08:00 and 09:00 a.m. after overnight fasting. Peripheral venous blood was collected into sterile vacuum blood-collection tubes without any additives, if serum samples, and into K3-ethylenediaminetetraacetate (EDTA) vacutainer tubes, if plasma samples (Becton–Dickinson, San Jose, CA, USA). Serum was separated after centrifugation at 4 °C, 1500×*g* for 10 min.

After separation into aliquots, serum and plasma samples were immediately analyzed or frozen and stored at 80 °C pending analysis. Only one thawing was allowed.

### Biochemical measurements

For the quantitative measurement of human COMP in serum, we used a commercial in vitro enzyme-linked immunosorbent assay kit (BioSource, Human COMP ELISA Kit, cat. no. MBS824705). The minimum detectable dose of human COMP is 10 pg/mL. The assay allows for the detection and quantification of endogenous levels of human COMP proteins within the linear range of 156–5000 pg/mL; samples were assayed in duplicate.

### Monitoring of toxicity

All patients were explicitly requested at each visit to report any eventual side effect. Monitoring of serum creatinine and calcium was used as index of safety.

### Statistical analysis

Considering the pilot nature of the study, no formal sample size estimation was performed. The planned sample size of 40 participants was established according to the enrolment ability of the participating centers. Patient allocation to treatment groups was managed centrally.

Statistical analysis was performed using GraphPad Prism v 6.01 software (GraphPad Inc., La Jolla, CA, USA). Results were expressed as mean ± standard deviation (SD). Differences between two groups were evaluated using Unpaired Student's *t* test. Analysis of variance (ANOVA) was used for comparisons of multiple groups followed by Tukey's hoc test. $P < 0.05$ was considered statistically significant.

## Results

Baseline characteristics of the enrolled patients are shown in Table 1. Twenty-four patients were enrolled in group A (2 men and 22 women, mean age 70 years) and 16 in group B (1 man and 15 female, mean age 69 years). The flow chart of the study is shown in Fig. 1.

Twenty-one (out of 24) patients in group A completed the planned 6 months of therapy, whereas 10 (out of 16) patients in group B completed 6 months of observation. These patients were analyzed for primary outcome.

None of the 40 enrolled patients reported side effects. In group A, a patient withdrew at month 2 because of the impossibility to reach our institute; 3 other patients withdrew at month 3 because of a transient ischemic attack, acute sciatica, and polymyalgia rheumatica, respectively. In group B, there were 6 withdrawals; they were patients who did not comply with the inclusion criteria changing usual drug or its dose.

In group A, after 6 months of therapy with CLO, we observed a significant reduction in the consumption of anti-inflammatory and analgesic drugs ($p < 0.0001$), number of tender joints ($p = 0.0097$), number of swollen joints ($p = 0.0251$), pain measured with VAS score ($p < 0.0001$), morning stiffness in minutes ($p = 0.0272$) and Dreiser's score ($p = 0.0119$). The number of deformed joints—as expected—did not change; on the contrary, hand strength improved at the right side (+ 35%, $p = 0.0465$) and at the left side (+ 38%, $p = -$n.s.), and both physician's global assessment of disease activity ($p < 0.001$) and patient's global assessment of disease activity decreased ($p < 0.0001$) (Fig. 2). Differences between

**Table 1** Main baseline characteristics of the enrolled patients in both groups

| Group | Number | Age (years-median, range) | Number of tender joints (mean ± SD) | Number of swollen joints (mean ± SD) | Pain (VAS score) | Dreiser score (mean ± SD) | Analgesic or anti-inflammatory drugs/month | COMP (pg/mL) |
|---|---|---|---|---|---|---|---|---|
| A (CLO) | 24 | 70.25 (47–85) | 9.44 ± 5.07 | 3.08 ± 2.30 | 6.92 ± 1.65 | 11.68 ± 5.77 | 12.68 ± 8.31 | 2029 ± 502 |
| B (control) | 16 | 69.5 (55–77) | 10.5 ± 4.71 | 2.80 ± 1.31 | 6,13 ± 1.46 | 11.5 ± 6.48 | 15.31 ± 8.44 | 1927 ± 355 |

groups A and B evaluated over a 6-month period showed a pain-decreasing trend for group A ($p = 0.018$) and a slightly increasing one in group B ($p$ = n.s.). Physician's and patient's global assessments of disease activity showed a strong reduction in group A ($p < 0.001$) (Fig. 2) .Concerning biochemical measurements, we observed no significant changes in levels of all markers evaluated in both groups except for serum levels of COMP that showed a significant reduction in group A at month 6 ($p = 0.0029$) versus baseline while in group B, there was no significant change (Fig. 3).

## Discussion

Here, we demonstrated that intramuscular CLO in active painful EOA of the hand is effective in reducing pain. The functionality of both hands was improved as demonstrated by the increased hand strength and reduction of disability by Dreiser's score. As a consequence, the consumption of anti-inflammatory or analgesic drugs significantly decreased. The present data confirm the results of a previous trial on CLO with a 24-month follow-up [15]. In that paper, 24 patients affected by EOA were treated with an attack 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. The results were as follows: pain reduction ($p < 0.001$), Dreiser's score reduction ($p = 0.012$), number of tender joint reduction ($p = 0.011$), strength of right hand improvement ($p = 0.04$), strength of left hand improvement ($p = 0.016$), physician's global assessment improvement ($p < 0.001$), and patient's global assessment improvement ($p = 0.021$). Therefore, CLO at the dosage of 200 mg/ampoule/day for 10 days is equivalent to i.v. CLO at the dose of 300 mg/day for 7 days, while CLO at the i.m. dose of 200 mg/day for 6 days is equivalent to i.m. CLO at the dose of 100 mg/day for 14 days. Moreover, i.m. CLO ampoule at the dose at 200 mg/day can substitute the intravenous administration that currently needs a day-hospital admission overcoming about 2–3 hours of infusion because of risk of renal failure.

Given the evidence of a direct interaction between cartilage and subchondral bone, the alterations in subchondral osteoblast metabolism are probably important causes of OA [2, 26, 27]. The early changes in subchondral bone can predict symptoms and cartilage damage. Recent findings show an increased bone resorption in the subchondral bone due to osteoclast activation followed by osteoblast/osteocyte involvement in later stages [2]. Moreover, chondrocytes of the articular surface have a limited capacity to repair and modify the surrounding extracellular matrix in comparison to skeletal cells in bone [28]. These are the main reasons why BPs have been proposed for the treatment of OA. A recent meta-analysis of 15 studies including 3566 participants treated with BPs for OA showed that BPs significantly improve pain, stiffness, and function;

moreover, BPs reduce osteophyte score and accelerate functional recovery [29].

In particular, zoledronate at the dosage used for the treatment of osteoporosis was demonstrated to be effective in increasing the osteoblast metabolic activity [30] and neridronate can modify the metabolic activity of human osteoblasts, suggesting the use of this BP for treating diseases with altered osteoblast metabolism [31, 32].

The reasons of the efficacy of CLO in EOA are the following: (i) CLO, differently from amino-BPs, where the block of mevalonate way induces the accumulation of intermediates able to activate circulating cytokines, has an anti-inflammatory activity. CLO reduces the release of inflammatory cytokines (IL-1b, IL-6, TNF-$\gamma$), of cyclooxygenase 2 and consequently of prostaglandin E (PGE). Moreover, CLO inhibits the matrix metalloproteinase-1 (MMP-1) [33–35]. (ii) Intra-articular CLO containing liposomes is able to induce synovial macrophage depletion in rheumatoid arthritis patients [36]; (iii) CLO has a central and peripheral prolonged antinociceptive activity, greater than that of acetylsalicylic acid. The analgesic action is independent of the antiresorptive effects on bone possibly via an interaction with neurons [37, 38]; CLO exerts analgesic effects by acting on glutamate- and/or ATP-related pain transmission pathways [39]. (iv) CLO reduces symptoms in knee osteoarthritis and is effective in preventing the mobilization of knee and hip prosthesis where the bone loss is probably the cause of the pain [40–42]. (v) CLO is able to induce an anabolic effect on articular chondrocytes which results in 90% increase in extracellular

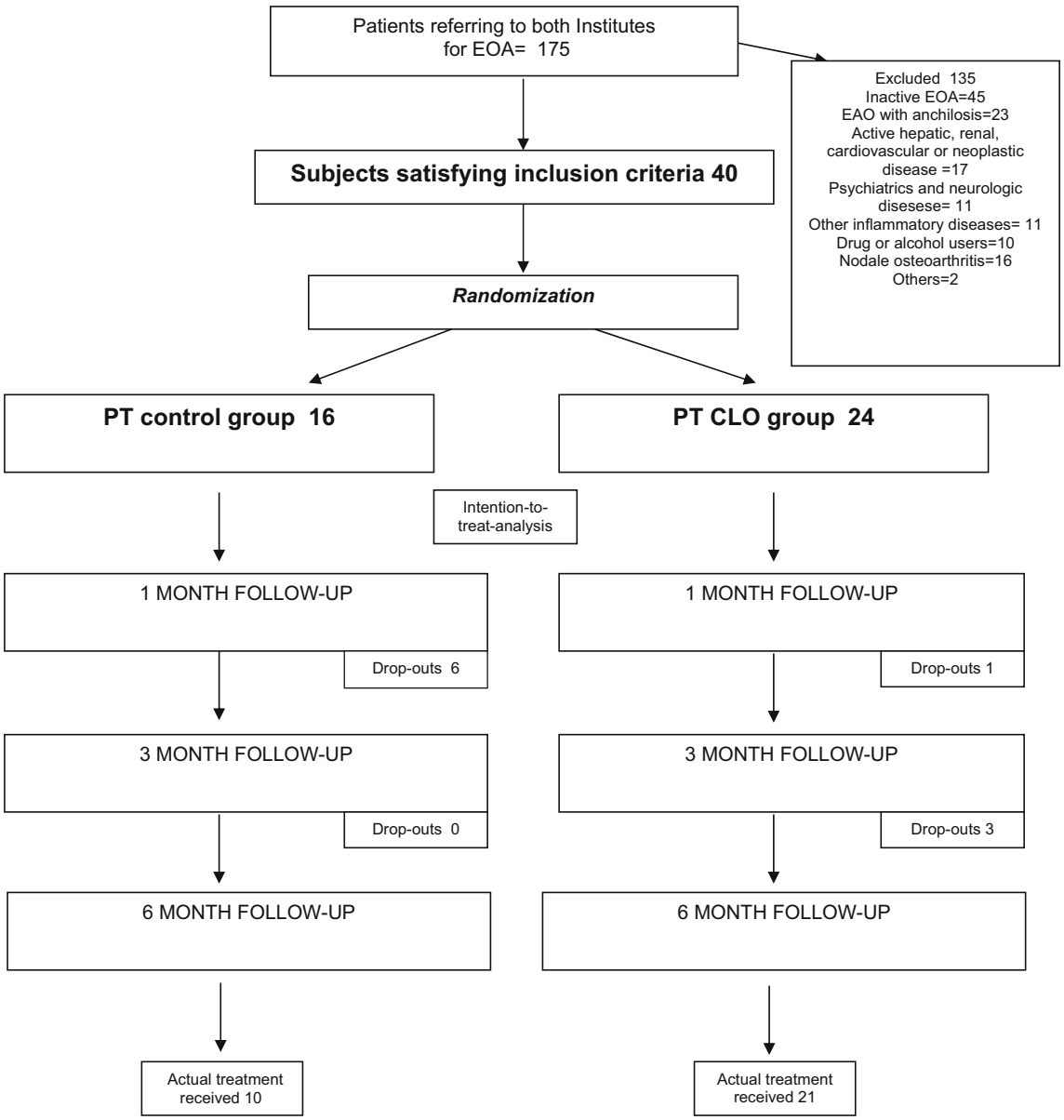


**Fig. 1** IM clodronate in erosive osteoarthritis of the hand (the ERODE study). Flow-chart. Details of the formation of the study group

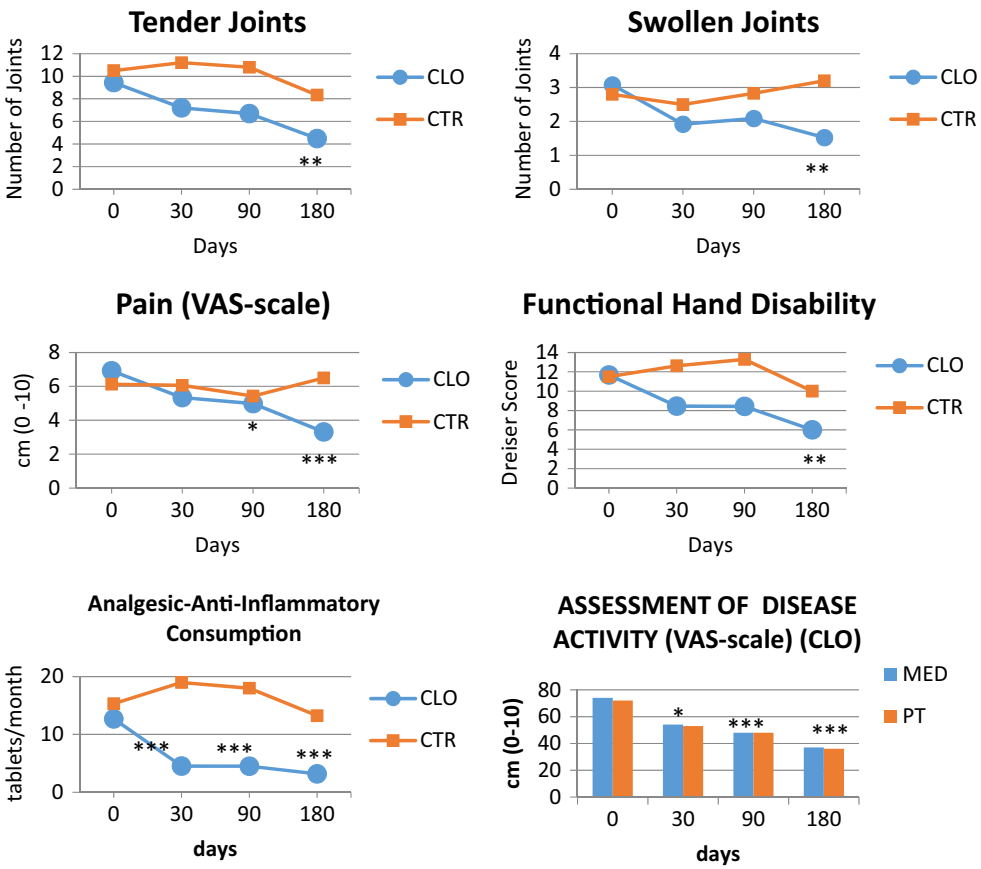


**Fig. 2** Main outcomes. *CLO*= clodronate group, *CTR*= control group, *MED*= phisician'global assessment of disease activity (measured on VAS-scale), *PT*= patient's global assessment of disease activity (measured on VAS-scale)

matrix accumulation [43]. (vi) CLO inhibits angiogenesis in vitro and in vivo and could be used to treat angiogenesis-dependent diseases including chronic inflammatory diseases [44].

The second point of the discussion is the significant reduction of serum levels of COMP observed at 6 months in the patients treated with CLO. COMP is considered as a promising biomarker of osteoarthritis. There are data showing that COMP serum levels are correlated to the presence of synovitis [45], to osteoarthritis severity [46], to the extension of the disease, to alterations in the subchondral bone turnover [47] and to radiographic progression [48, 49]. In particular, Aslam recently showed that there is a significant association between serum COMP levels and hand pain and function in patients with hand osteoarthritis ($p$ = 0.003). The Johnston County Osteoarthritis Project studied hand osteoarthritis in 663 patients evaluated with the AUSCAN scale (Australian-Canadian Hand Osteoarthritis index), a self-report 15-item questionnaire that assessed hand symptoms, and concluded that COMP was significantly higher in patients with a worse score for pain and function [50].

Our data are consistent with those published by Aslam [50] concerning both pain-disability reduction and serum COMP decrease. As COMP reflects the severity of hand osteoarthritis, its reduction could suggest that CLO is probably able to decrease in the progression of EOA by acting in the cartilage, in the subchondral bone and in the synovia.

## Study limitations

The small sample size, due to the nature of a pilot study, is the major limitation of the study.

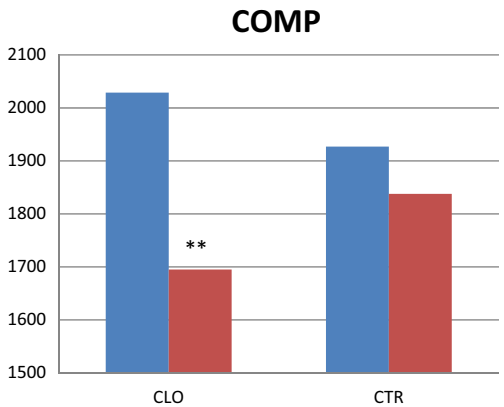


**Fig. 3** Serum COMP changes at 6 months versus baseline (pg/mL). *CLO*= clodronate group, *CTR*= control group

## Conclusions

We showed that intramuscular CLO is effective in the treatment of active painful erosive osteoarthritis of the hand. CLO is able to reduce pain and to decrease the pain-related disability. The reduction of serum COMP in our patients suggests that CLO in EOA is not only a symptomatic drug but could also play a role as a disease-modifying drug. Further studies involving a larger sample of patients are needed to confirm this intriguing hypothesis.

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Clinical analysis: Lorella Campostrini and Silvano Sacco.

Statistics: Silvano Sacco.

Protocol development: Gianantonio Saviola.

Manuscript preparation: Gianantonio Saviola, Luca Dalle Carbonare, and Silvano Sacco.

**Compliance with ethical standards**

**Disclosures** None.

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