EFFECTS OF CLODRONATE ON SYNOVIAL FLUID LEVELS OF SOME INFLAMMATORY MEDIATORS, AFTER INTRA-ARTICULAR ADMINISTRATION TO PATIENTS WITH SYNOVITIS SECONDARY TO KNEE OSTEOARTHRITIS

R. Cocco, C. Tofi, A. Fioravanti, F. Nerucci, *F. Nannipieri, *A. Zampieri, *S. Rosini, R. Marcolongo

Institute of Rheumatology, University of Siena,
*Department for Research and Development, Clinical Researches, Abiogen Pharma, Pisa

INTRODUCTION

It is now widely accepted that osteoarthritis cannot be considered as a simple age related modification of cartilage, but as a complex disease representing the final outcome of cartilage degeneration, abnormal subchondral bone remodelling and early inflammatory involvement. Therefore, strong interactions among condrocytes, synovia and subchondral bone occur, by means of active intervention of cytokines, phlogistic mediators, growth factors and proteolytic enzymes. Furthermore, the role of hydroxyapatite crystals seems to be also important in the progression of the inflammatory damage. Dichloromethylene bisphosphonate (C12MBP), or clodronate, is a compound which, like the other members of bisphosphonates, shares the activities of the analogue pyrophosphate: they have high affinity for solid phase calcium phosphate and, consequently, strongly bind to hydroxyapatite. Because of its physico-chemical and pharmacodynamic properties, clodronate is effective in the treatment of diseases characterised by elevated bone turnover, such as Paget's disease of bone, tumoral osteolysis and various kinds of osteoporosis. Even if clodronate's main mechanism of action deals with the activity on calcium phosphate crystals, effects on metabolic events in cells

involved in turnover of bone and cartilage, as well as effects on local inflammatory reactions, have been described (1). In fact, experimental reports showed that clodronate is able to stimulate the biosynthesis of collagen and proteoglycans (2) and to inhibit metalloproteinases activity, prostaglandins production in human cells cultures and interleukin-1 synthesis in vitro (3-5). Moreover, clodronate showed anti-inflammatory properties in adjuvant arthritis model and reduced free radical production by human activated neutrophils (6). These experimental evidences represented the rationale for testing the clinical efficacy and tolerability of locally administered clodronate in the treatment of osteoarthritis.

MATERIALS AND METHODS

This study was an open, non comparative, pilot trial. Twenty patients, 7 males and 13 females, aged betveen 51 and 70 years (mean age 63.4 years), affected by synovitis secondary to knee osteoarthritis were enrolled. Eligible patients were excluded in case of concomitant severe diseases, or if they had been treated with antinflammatory drugs in the previous 14 days, with intra-articular therapy within three months, or with bisphosphonates within the twelve months preceding the study. Patients underwent a cycle of six intra-articular injections of clodronate 0.9 mg, over a period of 21 days (day 1, 3, 7, 10, 14 and 21). At the same visits, spontaneous pain and pain on active movement were evaluated by means of a 100 mm visual analogue scale (VAS). At day 1, 3, 7, 10 and 21 synovial fluid samples were taken to assess prostaglandin E2 (PGE2), leukotriene B4 (LTB4) and tromboxane B2 (TXB2) levels, by ELISA. At baseline and at the end of the study, RBC, WBC with differential count, ESR, CRP, serum creatinine, serum calcium and urinalysis were measured for a global evaluation of tolerability. Mean values of pain, measured by VAS, have been compared by means of Friedman two-way Anova. Comparisons between visits and baseline values have been performed through Wilcoxon test. Finally, correlations between pain evolution and synovial fluid parameters variations have been studied.

RESULTS

Clinical results attested a marked improvement of patient's symptomatology over the study period. In particular spontaneous pain compared to baseline levels resulted significantly lower ($p<0.05$) at day 3 and the statistical difference was maintained up to the end of the trial (fig. 1). Changes over time of pain on active movement also showed an immediate trend to decrease, which became statistically significant ($p<0.05$) at day 10 (fig. 2). Laboratory evaluation of synovial fluid inflammatory mediators indicated that PGE2, but not LTB4 and TXB2, resembled the clinical evolution of pain. Linear regression analysis confirmed a correlation ($Rsq=0.700$; $p<0.05$) between the pain decrease and the bisphosphonate induced reduction of PGE2 levels (fig. 3). The measurement of routine laboratory parameters did not evidence any abnormality and no adverse event was reported during the study. The drug was, therefore, very well tolerated both locally and sistemically.

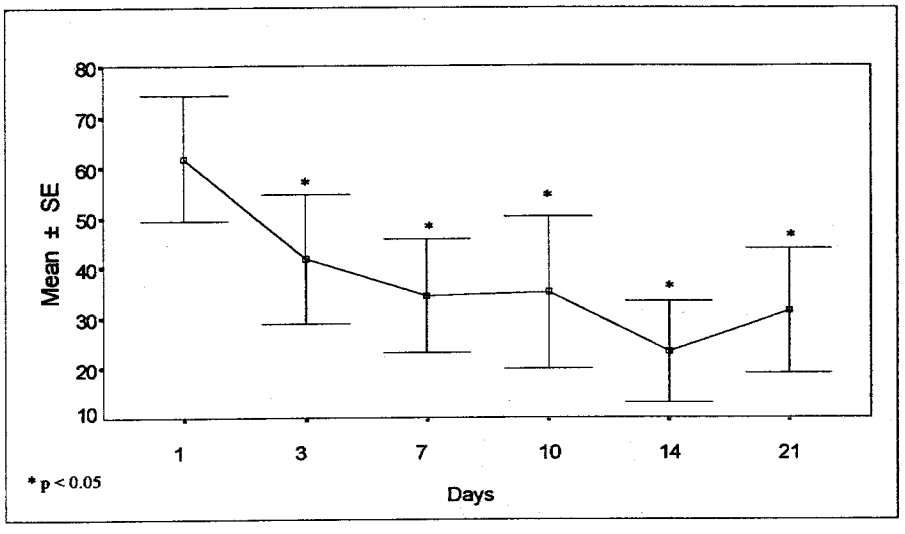

Fig. 1 - Spontaneous pain (mm).

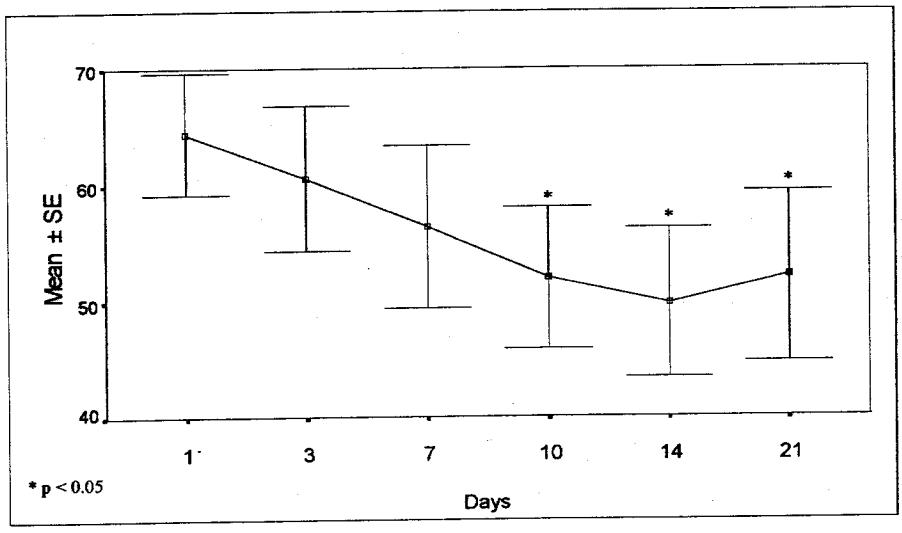

Fig. 2 - Pain on active movement.

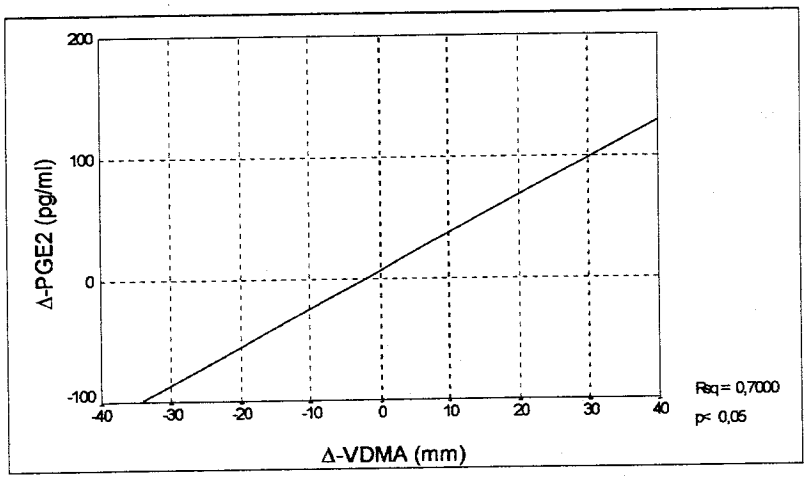

Fig. 3 - Correlation between clodronate induced variation of PGE2 synovial fluid levels (Δ-PGE2) and pain (Δ-VDMA).

DISCUSSION

Pre-clinical laboratory evidences suggest the potential use of bisphosphonates and clodronate in particular, in the therapy of osteoarthritis (3,4). In the only clinical study previously carried out in patients with osteoarthritis (7), clodronate was compared to metyl-prednisolone acetate: the results showed that the administration of intra-articular clodronate caused a decrease of both spontaneous pain and pain on active movement which was absolutely comparable to that induced by steroid. In the present trial the same intraarticular regimen of clodronate led to a clinical response which was similar in extent, confirming the effectiveness of the drug in improving the clinical status of the patients, especially in case of inflammatory flares, by means of a reduction of pain. At this regard, it is relevant the pharmacodynamic finding of a correlation between pain reduction and the bisphosphonate induced decrease of a flogistic mediator, which confirms the capability of clodronate to affect, although indirectly, PGE2 levels in vivo. It is to underline that the open design of the study does not allow definitive conclusions about the "antinflammatory" action of clodronate in this kind of disease. Nevertheless, the outcomes obtained on clinical parameters, together with the biochemical data, suggest the need for further, double blind, phase three trials, which could be helpful to determine the real advantages of clodronate over the other, common, intra-articular therapies.

Recent studies have outlined the role of bisphosphonates, and particularly clodronate, as potential therapeutic agents for inflammatory and degenerative joint diseases. On this basis, we carried out an open, non comparative pilot trial to evaluate the effects of clodronate on synovial fluid concentration of some inflammatory mediators (prostaglandin E2, leukotriene B4 and tromboxane B2) after intra-articular, repeated administrations in 20 patients (7 males and 13 females) with synovitis secondary to knee osteoarthritis. At the end of the treatment period, statistically significant reductions ($p<0.05$) of spontaneous pain and pain

on active movement, evaluated by means of a 100 mm visual analogue scale (VAS), were reported. Linear regression analysis showed that the decrease of pain was correlated with the bisphosphonate induced reduction of prostaglandin E2 levels. These results, in spite of the limitation due to the open design of the trial suggest a possible role of bisphosphonates in the treatment of knee osteoarthritis.

---

1) HUGHES D.E. et al., J. Bone Miner. Res., 1995, 10, 1478-1480.
2) GUENTHER H.L., GUENTHER H.E., FLEISCH H., Biochem. J., 1981, 196, 293-301.
3) TERONEN O. et al., Calcif. Tissue Int., 1997, 61, 5941.
4) MC GUIRE M.K.B., RUSSEL R.G.G., MURPHY G., REYNOLDS J.J., Ann. Rheum. Dis., 1981, 40, 515-529.
5) EVEQUOZ V., TRECHSEL U., FLEISCH H., Bone, 1985, 6, 439-444.
6) DUNN C.J., DOYLE D.V., WILLOUGHBY D.A., Drug Dev. Res., 1993, 28, 47-55.
7) MINISCHETTI G., TRASCIATTI S., ROSINI S., Giorn. It. Ric. Clin. Ter., 1993, 14, 155-159.

KEY WORDS: clodronate, osteoarthritis collagenase, prostaglandin E2.

Lectured at the meeting held in Siena on October 5, 1999.
Received: October 12, 1999; accepted October 29, 1999.

Address reprint requests/correspondence to Prof. R. Marcolongo, Institute of Rheumatology, University of Siena, Policlinico Le Scotte, Viale Bracci 1, I-53100 Siena.