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Effect of oral clodronate on structural damage and bone turnover in rheumatoid arthritis

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ABSTRACT

Objective. *To study the effect of oral clodronate on structural damage and bone metabolism in rheumatoid arthritis (RA).*

Methods. *In this 2-year proof-of-concept study, sixty patients with at least moderately active RA were randomised to receive anti-rheumatic therapy alone or together with oral clodronate 1600 mg daily. Radiographs of hands and feet and serum samples for bone biomarkers were studied at baseline and at 24 months.*

Results. *At 24 months, progression of radiographic joint damage was similar in the 2 groups. Clodronate suppressed carboxyterminal cross-linked peptide of type I collagen (p=0.03) and aminoterminal propeptide of type I procollagen (p=0.01). Eight patients (27%) withdrew from clodronate therapy due to adverse drug reactions.*

Conclusion. *Oral clodronate did not retard the focal bone damage in RA despite its beneficial effect on overall bone metabolism, as judged by the decrease in the reference bone biomarkers.*

Introduction

Bone erosions are a radiographic hallmark of rheumatoid arthritis (RA) and reflect poor prognosis. Several lines of evidence implicate the osteoclast as the effector cell in the pathogenesis in all forms of bone damage in RA (1, 2). Bisphosphonates inhibit generalised bone loss and their main target is the osteoclast. Hence, their potential for preventing focal bone damage in RA has evoked interest. Clinical RA trials have, however, produced disappointing results (3). In a proof-of-concept study of 39 RA patients zolendronic acid (ZA) did significantly decrease the number of new erosions as assessed using magnetic resonance imaging (MRI) (4). The proinflammatory effects of the potent amino-bisphosphonates, such as ZA, might, on the other hand, be a drawback when these drugs are used in the treatment of inflammatory joint disease (1, 3, 5). The less potent non-amino-bisphosphonates, such as etidronate and clodronate are not pro-inflammatory and decrease bone destruction in animal models of arthritis (3, 5). In our own previous study cyclical intermittent etidronate did not prevent progression of radiographic joint damage in moderately active RA (6). Clodronate, unlike etidronate, can be administered continuously and might thus have greater potential as an inhibitor of the pathologic bone resoprtion associated with joint inflammation. The aim of the present study was to evaluate the ability of clodronate to slow down the development of structural damage in RA. The effect of clodronate on overall bone metabolism was monitored using reference bone biomarkers: serum carboxyterminal cross-linked peptide of type I collagen (s-Ctx) and serum aminoterminal propeptide of type I procollagen (s-PINP) (7).

Patients and methods

Patients

The study group comprised 60 patients fulfilling the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA. Inclusion criteria were: age ≥18 years, ≥4 swollen joints at baseline, elevated C-reactive protein (CRP) (≥15 mg/l) or erythrocyte sedimentation rate (ESR) (≥19 mm/h) either at baseline or within the previous 12 months. Patients previously treated with BPs and those who at baseline were judged to require BP treatment due to osteoporosis were excluded. Other exclusion criteria were pregnancy/breastfeeding and impaired renal function (serum creatinine >115 μmmol/l). Eligible patients were enrolled between May 2003 and June 2005.

Study design

This investigator-initiated, randomised, parallel-group, controlled, open label and evaluator blinded (radiology, bone biochemistry) study was conducted at Helsinki University Central Hospital, with the approval of the local Medical Ethics Committees. Informed consent was obtained from all patients. After baseline assessment patients were randomly allocated to one of 2 treatment groups. Clodronate group (n=30) received Clodronate (BONEFOS®, Bayer Schering Pharma Oy, Finland) 1600 mg daily in conjunction with antirheumatic therapy. Control group (n=30) received

Table I. Demographic and clinical characteristics of all enrolled patients by treatment group.

	Clodronate group (n=30)	Control group (n=30)
Age, mean ± SEM (years)	52.5 ± 2.2	55.2 ± 2.2
Males/females	6/24	9/21
Menopausal status (yes/no)	15/9	14/7
HRT/postmenopausal women	3/15	6/14
Disease duration, mean ± SEM (years)	6.8 ± 1.0	7.6 ± 1.0
Glucocorticoid use, n. (%)	12 (40)	13 (43)
DAS28, mean ± SEM	4.0 ± 0.2	3.8 ± 0.2
CRP, mean ± SEM (mg/l)	12.8 ± 2.2	9.0 ± 1.4
ESR, mean ± SEM (mm/h)	20.0 ± 2.4	17.2 ± 2.6
Total Sharp score		
Mean ± SEM	21.4 ± 4.6	30.6 ± 8.2
Median, range	9 (0-85)	12 (0-205)

HRT: hormone replacement therapy; DAS28: Disease activity score using 28-joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table II. Radiographic scores and variables of disease activity at baseline and changes at 24 months in the clodronate group (n=30) and the control group (n=29). Mean ± SEM.

Variable	Baseline	Change at 24 months	*p*-value
Total Sharp score			0.75
Clodronate	21.4 ± 4.6	5.5 ± 1.2	
Control	30.5 ± 8.2	5.9 ± 1.3	
Erosion score			0.91
Clodronate	15.6 ± 3.1	3.8 ± 0.9	
Control	21.2 ± 5.1	3.9 ± 0.9	
JSN-score			0.68
Clodronate	5.7 ± 1.5	1.7 ± 0.6	
Control	9.3 ± 3.4	2.0 ± 0.5	
DAS28			0.17
Clodronate	4.0 ± 0.2	-1.2 ± 0.2	
Control†	3.8 ± 0.2	-0.7 ± 0.2	
CRP (mg/l)			0.17
Clodronate	12.8 ± 2.2	-5.4 ± 2.5	
Control†	9.3 ± 1.5	-2.8 ± 1.5	
ESR (mm/h)			0.22
Clodronate	20.0 ± 2.4	-4.7 ± 2.0	
Control†	17.2 ± 2.6	-1.2 ± 2.4	

JSN-score: joint space narrowing score; DAS28: Disease activity score using 28-joint count CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; † n: 28.

only anti-rheumatic therapy. Changes to the concomitant therapy with disease-modifying anti-rheumatic drugs (DMARDs) and/or oral steroids could be made whenever considered appropriate throughout the study period in both groups.

Outcome assessments

The patients were assessed at baseline and at 24 months. The following disease parameters were determined: ESR, CRP and the Disease Activity Score based on 28-joint counts (DAS28) (8). Serum samples for bone biochemistry assessments were collected at baseline and at 24 months and stored at -20°C. Automated chemiluminescence assay (CLIA) was used to measure serum PINP (IDS-iSYS Intact PINP, Immunodiagnostics Systems, Boldon, UK). The automated PINP method was validated recently (9). The ELISA method for the measurement of serum CTx (Serum CrossLaps, Immunodiagnostics Systems, Boldon, UK) has been described elsewhere (10). All determinations were done in duplicates.

Plain posteroanterior radiographs of hands and feet were obtained at baseline and at 24 months and were scored in a chronological order according to van der Heijde's modification of Sharp's method (11) by one experienced reader (LL) who was unaware of the treatment assignments.

Statistical analyses

Statistical analysis was done with SPSS 16.0 software. Changes in response variables from baseline to 24 months were compared between treatment groups using Mann-Whitney U-test. The relation between variables was measured by using χ^2 test or Spearman's rank correlation coefficient. The significance level was set at $p<0.05$.

Results

Subjects.

Demographic and baseline characteristics presented in Table I were generally comparable between treatment groups. 58 of the 60 enrolled patients entered the 2-year visit. Two patients in the control group did not enter the termination visit due to severe co-morbidity (2-year radiographs were obtained for the other of these two). Both baseline and 2-year x-rays of hands and feet were available in 59 patients. Paired serum samples for bone biochemistry markers were available in 25 patients both in the clodronate and control groups. Eight patients withdrew from clodronate therapy due to adverse drug reactions. They were included in the intent-to-treat analysis of radiographic progression but were excluded from the analyses of bone biomarkers as they did not take clodronate during the second year of the study. In 22 out of 30 patients (73%) in the clodronate group the estimated adherence to clodronate expressed as medication possession ratio (MPR) was ≥65% and in 18 (60%) ≥80%. Two patients randomised to the placebo group were later due to osteopenia ordered aminobisphosphonate by their general practitioner. These two patients were included in the analysis of radiographic progression but were excluded from the analyses of bone biomarkers. 5 patients started biologic DMARD therapy during the study, 3 in the clodronate group and 2 in the control group.

Efficacy

In both treatment groups there was a significant increase in all 3 mean radiographic scores (Table II). The change over time was not different between the 2 groups. This result was the same if, in the clodronate group, only patients with MPR ≥80% were included to analyses. The erosion score increased by 3.4±1.2 (mean ± SE) in this subgroup. The proportion of patients with progression of erosions was not different between the two groups (70% in the clodronate group vs. 69% in the control group; p=0.93). Also in the per-protocol population the proportion of patients with progression of erosions was similar in the two groups (13/18 [72%] in the clodronate group and 18/27 [67%] in the control group) (p=0.69). There was a slight decrease in clinical disease activity in both treatment groups. During the study the changes in CRP, ESR or DAS28 were not different between the two groups (Table II).

Compared to the control group, the markers of bone turnover decreased significantly in patients in the clodronate group (Table III). The progression of radiographic scores did not correlate to the baseline values of bone biomarkes or to change of these markers during the study (data not shown).

Safety

In the clodronate group gastrointestinal disorders were reported by 7 patients (23%), 6 of whom withdrew from clodronate therapy. One patient withdrew from clodronate because of increasing joint pain and one patient due to bullous pemphigoid. The causal relationship between this skin disorder and clodronate was, however, considered unlikely. Three new malignancies were detected during the study, one in the clodronate group (colon cancer) and 2 in the control group. The patient diagnosed with colon cancer had earlier withdrawn from clodronate due to diarrhoea.

Table III. Bone biomarkers at baseline and percentage changes at 24 months in the clodronate group (n=20) and the control group (n=23). Median (IQR).

Variable	Baseline	Percentage change at 24 months	p-value
CTx ng/ml			0.03
Clodronate	0.25 (0.21)	-40.3 (67.7)	
Control	0.28 (0.23)	-10.8 (51.1)	
PINP mg/l			0.01
Clodronate	49.6 (25.6)	- 36.4 (41.6)	
Control	39.7 (41.8)	- 14.4 (51.2)	

CTx: carboxyterminal cross-linked peptide of type I collagen; PINP: aminoterminal propeptide of type I procollagen.

Discussion

The result suggests that oral clodronate 1600 mg daily does not retard progression of radiographic damage in RA despite its favourable effect on systemic bone loss as judged by the significant decline in bone biomarkers.

In rheumatoid arthritis it is well established that joint damage increases with increasing disease activity (12). Accordingly, patients eligible to this trial required to have at least moderate disease activity. Results from clinical trials, including a recent RA study with denosumab (13), however, indicate that in a drug intervention trial disease activity and progression of joint erosions may be dissociated. Therefore, we believe that the open-label approach and the unrestricted use of background DMARD therapy do not significantly bias the outcome of this study. On the other hand, the study was underpowered and the negative result regarding the anti-erosive effect of clodronate could be related to the small number of patients.

In our previous etidronate study change in collagen type I degradation marker, serum NTx, correlated with the progression of the erosion score in patients with recent onset RA (6). A range of biochemical markers, including a specific marker of type I bone collagen breakdown, were recently shown to be useful predictors of radiographic progression in early RA (14). In contrast, no association between bone biomarkers and increase in erosion score was now observed. The small number of patients but also the longer disease duration at baseline in the present study may explain this difference to earlier studies.

Apart from the preliminary results for i.v. ZA, the evidence that bisphosphonates may prevent erosions in RA is lacking. That the osteoclast is an important therapeutic target in RA is, nevertheless, emphasised by a recent trial with denosumab in which RANKL inhibition prevented progression of erosion scores in patients with active RA. Differences in the mode of action and pharmacokinetic properties between bisphosphonates and denosumab (15) could, on the other hand, play a role in the evaluation of the ability of different antiresorptive therapies to prevent inflammatory bone loss.

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