

Treatment with tiludronate has a similar effect to risedronate on Paget's disease activity assessed by bone markers and bone scintigraphy

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Abstract

Objective

To compare the effects of tiludronate and risedronate on Paget's disease activity assessed by biochemical markers of bone turnover and quantitative bone scintigraphy.

Methods

An open-labeled non-randomized study was performed in 49 patients with Paget's disease who had completed treatment with tiludronate (400 mg/d) for 3 months (28 patients) or risedronate (30 mg/d) for 2 months (21 patients). Biochemical markers of bone turnover, including serum total alkaline phosphatase (TAP), bone alkaline phosphatase (BAP), procollagen type I N propeptide (PINP) and urinary N-terminal cross-linking telopeptide of type I collagen (NTX) were measured at baseline and at 6 and 12 months after the end of treatment. Quantitative bone scintigraphy at baseline and 6 months after the end of treatment was performed in all patients obtaining a scintigraphic activity index (SAI).

Results

At baseline there were no significant differences in disease activity between both groups of patients, since markers of bone turnover as well as SAI were similar in both groups. The effects of tiludronate and risedronate in reducing the biochemical markers of bone turnover were comparable at 6 months (tiludronate vs risedronate: TAP -52% vs -43%; BAP -69% vs -56%; PINP -68% vs -63%; NTX -62% vs -59%) and at 12 months after the end of treatment (tiludronate vs risedronate: TAP -47% vs -36%; BAP -57% vs -46%; PINP -57% vs -52%; NTX -51% vs -52%). The effects of tiludronate and risedronate on SAI were also similar 6 months after the discontinuation of treatment. In addition, the percentage of patients who showed normalized serum TAP levels at 6 months after treatment were similar with both agents (74% with tiludronate and 70% with risedronate).

Conclusion

Tiludronate and risedronate given at the currently recommended dosages induce similar responses in Paget's disease activity.

Key words

Therapy, bisphosphonates, bone turnover.

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Introduction

Paget's bone disease is a localized disorder characterized by increased and disorganized bone remodeling which can lead to bone pain and deformity (1). The principal strategies for treating Paget's disease are aimed at suppressing the increased osteoclastic activity and bisphosphonates, especially the new compounds, are the treatment of choice for this disorder. These agents have been shown to effectively decrease the disease activity for prolonged periods of time in most patients (2). Generally, nitrogen-containing bisphosphonates such as risedronate, alendronate, pamidronate or zoledronic acid, are considered to be more potent agents for treating Paget's disease than non-nitrogen containing bisphosphonates, such as etidronate, clodronate and tiludronate (3-5). Indeed, tiludronate has been considered a relatively weak antiresorptive agent, only slightly more potent than etidronate for treating this process (4, 5). By contrast, risedronate is considered to be the leading bisphosphonate in current use, although recent data indicate that a single infusion of zoledronic acid produces a more rapid and sustained response (6); with the exception of etidronate, there are no studies comparing tiludronate with other bisphosphonates in Paget's disease.

Biochemical markers of bone turnover are useful tools in assessing the effect of therapy on this disorder. Indeed, markers such as total and bone alkaline phosphatase (TAP, BAP), procollagen type I N propeptide (PINP) and N-terminal cross-linking telopeptide of type I collagen (NTX) have shown a high correlation with scintigraphic indices of disease activity, and they are also the most sensitive markers for monitoring disease activity (7-12). Although the indications of therapy and the response goals in this disorder are not clearly established, normalization of biochemical markers, especially of serum TAP, is considered the main end point in most studies.

Therefore, the aim of this study was to compare the effect of oral risedronate (a nitrogen-containing bisphosphonate, which is very often used in daily prac-

tice) with that of tiludronate (a seldom prescribed non-nitrogen containing bisphosphonate) on reducing Paget's disease activity assessed by measuring biochemical markers of bone turnover and quantitative bone scintigraphy.

Materials and methods

Subjects

Forty-nine patients with Paget's bone disease, 22 men and 27 postmenopausal women, aged 42-86 years (mean \pm SEM: 63.6 \pm 1.6 years) were included in the study. In all patients, plain radiographs and bone scintigraphy documented the diagnosis of Paget's disease. Twenty-seven patients (55%) had polyostotic disease. The indications for treatment were: symptomatic disease, serum TAP concentration of at least twice the upper limit of normal, and location where progression of the disease could lead to future complications. Patients with skull involvement were not included in the study because we have previously observed that this location is associated with differing behavior of biochemical markers (8, 13). Liver and kidney function tests were normal in all patients, and those who had been treated with calcitonin during the previous year or with bisphosphonates during the previous two years were not included in the study.

Reference values were obtained from a sample of 26 healthy volunteers of similar age and gender (15 men and 11 women, mean \pm SEM: 68.4 \pm 1.5 years) with no evidence of disturbances of calcium metabolism or metabolic bone disease.

All patients provided informed consent for participation and the Ethics Committee of the Hospital approved the study.

Study design

This was a prospective open-label study where patients were included consecutively to receive treatment with either oral tiludronate (400 mg/day for 3 months) or risedronate (30 mg/d for 2 months). All 49 patients included in the study were compliant with treatment and completed the trial. Patients were required to fast before and after treatment and were instructed to take

the drug with 200 ml of water (30-60 minutes before breakfast) and not to lie down for 1 hour after taking the tablets. Laboratory assessment was carried out on each patient before the start of treatment and at 6 and 12 months after discontinuation of therapy. Bone scintigraphy was performed at baseline and at 6 months after the end of treatment. The study end points were the comparison of the percentage decrease in the levels of bone markers and the percentage of patients who showed normalized serum TAP levels at 6 months after treatment with tiludronate and risedronate. The time point of 6 months was selected because we have previously observed the nadir response to tiludronate therapy at this time (7).

Biochemical determinations

Blood and second morning urine samples were obtained from each subject on the same day between 8:00 and 10:00 a.m. after an overnight fast. Serum and centrifuged urine samples were kept frozen at -20°C until analysis.

The serum bone formation markers measured were TAP (spectrophotometric kinetic assay, according to the recommendations of the Scandinavian Committee for Clinical Chemistry and Clinical Physiology, using DEA buffer in a DAX 72 analyser; Bayer Diagnostics Technicon, Tarrytown, NY, USA), BAP (Tandem-R Ostase; Beckman Coulter, Fullerton, CA, USA) and PINP (Intact PINP; Orion, Espoo, Finland). The urinary marker of bone resorption measured was NTX (Osteomark; Ostex International Inc, Seattle, WA, USA). Results of NTX determinations were expressed as a ratio to urinary creatinine. The intra-assay and inter-assay coefficients of variation for each marker were as follows: TAP 0.75% and 3.1%; BAP 3.5% and 8.8%; PINP 4.1% and 5.6% and NTX 5.5% and 9.2%. The intra-individual variabilities of bone markers obtained from patients with stable Paget's disease were as follows: TAP 12.4%; BAP 4.9%; PINP 10% and NTX 15.8%. The critical difference values obtained in these patients for TAP, BAP, PINP and NTX were 35%, 25%, 35% and 47%, respectively (9).

Table I. Characteristics of the pagetic patients and the control group at entry.

n	Controls	Tiludronate group	Risedronate group
Skeletal disease	27	28	21
		Polyostotic (57%)	Polyostotic (52%)
Age (years)	68 ± 1.5	62 ± 2.1	66 ± 2.5
TAP (U/L)	177 ± 6.3	685 ± 117	612 ± 106
BAP (ng/mL)	14 ± 0.8	90 ± 18.1	65 ± 14
PINP (ng/mL)	31 ± 1.9	240 ± 46	153 ± 19.4
NTX (nM/mM)	39 ± 3.6	284 ± 42.9	193 ± 32.3
SAI		9922 ± 1877	8368 ± 1909

TAP: total alkaline phosphatase; BAP: bone alkaline phosphatase; PINP: procollagen type I N propeptide, NTX: N-terminal cross-linking telopeptide of type I collagen; SAI: scintigraphic activity index. There were significant differences in all bone markers analysed between pagetic patients at baseline and controls.

Quantitative bone scintigraphy

Bone scintigraphy was performed 2 h after an intravenous injection of 740 MBq (20 mCi) of 99m-technetium-hydroxy-methylene bisphosphonate. Whole-body images were acquired simultaneously in both the anterior and posterior views using a dual-headed gamma camera (Helix, Elscint, Israel) and stored in a 512 x 512 matrix for quantitative analysis. From these data a scintigraphic activity index (SAI), which reflects both the extent and activity of the disease was obtained, as described elsewhere (10). The intraindividual variability of SAI was 4.5% and the critical difference value for this measurement was 13%.

Statistical analysis

Results are expressed as means ± SEM (standard error of the mean). Between-group comparisons were performed using the Mann-Whitney U-test. Differences between proportions were assessed by Chi-square test. All comparisons were made using a significance

level of 0.05. All statistical analyses were performed using SPSS software for Windows (version 10.0).

Results

A total of 49 patients were enrolled in the study, 28 in the tiludronate group and 21 in the risedronate group. Twenty-five patients had previously been treated with bisphosphonates; the number of patients who had previously been treated with bisphosphonates was similar in both groups: 12 patients (43%) in the group of tiludronate and 13 (62%) in the group of risedronate. At entry, all pagetic patients showed higher mean baseline values for all bone markers compared to controls, and no significant differences were observed between both groups of patients with respect to biochemical and scintigraphic indices of disease activity (Table I). After therapy, all biochemical markers analyzed in the study, as well as SAI, showed a significant decrease in both groups of patients when compared with baseline values (data

Table II. Percentage of changes in bone markers and SAI at 6 and 12 months after the end of therapy in both groups of patients.

	Patients treated with tiludronate		Patients treated with risedronate	
	6 months	12 months	6 months	12 months
TAP	-52 ± 3.9%	-47 ± 4.1%	-43 ± 4.3%	-36 ± 4.6%
BAP	-69 ± 3.3%*	-57 ± 4.3%	-56 ± 4.7%	-46 ± 5.7%
PINP	-68 ± 2.8%	-57 ± 4.2%	-63 ± 4.4%	-55 ± 4.7%
NTX	-62 ± 3.9%	-51 ± 5.9%	-59 ± 6.5%	-52 ± 6.2%
SAI	-46 ± 4%		-45 ± 4.6%	

For abbreviations see Table I.

*P=0.034 compared with risedronate group.

Table III. Mean values of bone markers and SAI and percentage of patients with normalization of TAP levels at entry and 6 months in both groups of patients according to previous treatment with bisphosphonates.

n	Tiludronate group		<i>P</i> *	Risedronate group		<i>P</i> *
	Previously treated 12	Untreated 16		Previously treated 13	Untreated 8	
At entry						
TAP (U/L)	748 ± 155	637 ± 173	0.04	553 ± 123	707 ± 197	NS
BAP (ng/mL)	101 ± 24	82 ± 27	0.04	64 ± 20	67 ± 18	NS
PINP (ng/mL)	257 ± 32	228 ± 77	0.03	150 ± 25	158 ± 30	NS
NTX (nM/mM)	376 ± 78	224 ± 46	NS	219 ± 49	152 ± 23	NS
SAI	11073 ± 1944	9077 ± 2968	NS	8918 ± 2647	7157 ± 2161	NS
After 6 moths						
TAP (U/L)	269 ± 35	209 ± 14	NS	283 ± 42	320 ± 101	NS
BAP (ng/mL)	24 ± 5	18 ± 2	NS	23 ± 4	28 ± 13	NS
PINP (ng/mL)	71 ± 11	54 ± 10	NS	44 ± 7	49 ± 18	NS
NTX (nM/mM)	83 ± 10	81 ± 10	NS	70 ± 15	67 ± 25	NS
SAI	6707 ± 1319	4489 ± 1544	NS	6161 ± 2332	4352 ± 2893	NS
Normalized TAP	58%	81%	NS	53%	87%	NS

For abbreviations see Table I.

*P**: *P* values between previously treated and untreated patients.

not shown). In general, the effects of tiludronate and risedronate in reducing the biochemical markers of bone turnover were similar, not only at 6 months but also at 12 months after the end of treatment (Table II). Only the percentage of reduction in serum BAP was slightly greater in patients treated with tiludronate at 6 months (Table II). The effect of tiludronate and risedronate on SAI was also similar (Table II). In addition, the percentage of patients who showed normalization of serum TAP levels at 6 months was comparable in both groups of patients: 74% of the patients showed normalized TAP levels with tiludronate, whereas 70% of the patients had normalized TAP levels with risedronate ($p = n.s.$).

When we analyzed the patients who had been previously treated with bisphosphonates separately, although the patients from the tiludronate group showed slightly greater values of markers of bone formation at baseline, the response to therapy was similar in both groups of patients (Table III). There were not significant differences in the percentage of normalized serum TAP levels between groups, however, patients previously untreated tended to have greater percentages of normalization of this marker after treatment with either tiludronate or risedronate (Table III). In addition, in the previously un-

treated patients (16 patients from the tiludronate group and 8 patients from the risedronate group) the response to therapy, evaluated by bone markers and SAI, was comparable in both groups of patients.

Discussion

This study shows that tiludronate and risedronate given at the currently recommended dosages induce a similar decrease in Paget's disease activity. Previous studies have shown a short-term response in bone turnover in a high number of patients with a similar percentage of reduction in bone markers after 3-6 months of therapy with oral bisphosphonates such as tiludronate, risedronate or alendronate (7, 8, 14-16). However, the percentage of normalization in serum TAP levels differs in these series, ranging from 77% in patients treated with risedronate to 27% in those treated with tiludronate (14, 16). There are various factors that can influence the response to therapy in Paget's bone disease, such as the disease activity at baseline (11, 17-19), the doses of the drug or previous treatments with bisphosphonates, among others (20, 21). Indeed, some patients may develop a resistance to the effect of bisphosphonates, especially when multiple courses of treatment with the same agent are performed (21, 22). In-

terestingly, such patients will usually respond well to the use of a different bisphosphonate (23).

Nitrogen-containing bisphosphonates such as risedronate, alendronate or pamidronate are considered to be more effective than tiludronate in treating Paget's disease (3-5). However, there are no comparative studies confirming this suggestion. The comparison of the therapeutic response of different bisphosphonates from different studies is difficult to make since these patients not only differ in the type of treatment they receive, but also in other factors that can influence the response to therapy. There are few comparative studies on bisphosphonates in pagetic patients, most of them comparing etidronate with several of the new bisphosphonates. In all these studies etidronate was less effective in decreasing the activity of Paget's disease than agents such as alendronate, risedronate and tiludronate (14, 16, 23). However, data comparing the effect amongst these new bisphosphonates are scarce. Thus, there is only one previous prospective study comparing the effect of intravenous pamidronate with oral alendronate in Paget's disease (24). In this study both drugs showed the same efficacy in achieving the biochemical remission of the disease in previously untreated patients; but in patients previously treated with

pamidronate, alendronate was more effective.

Recently, a comparative study of zoledronic acid with risedronate showed that zoledronic acid induces a greater and more sustained response in Paget's disease (6). In the present study we compared two distinct types of bisphosphonates, tiludronate and risedronate, and we observed similar effects in reducing the activity of the disease, not only in the percentages of decrease in bone markers and SAI but also in the percentage of patients who normalized serum TAP levels. Although the study was not randomized, it is important to point out that the clinical characteristics of both groups of patients were comparable at baseline. Nevertheless, in the Roux *et al.* study (16) only 27% of the pagetic patients showed normalized serum TAP levels after 6 months of treatment with tiludronate, a much lower figure than that observed in our series, which up to 74% of our patients showed. Although the reasons for such discrepancies are unknown, the baseline clinical differences between the patients included in both studies could partly explain these results. Thus, in the Roux *et al.* study, pagetic patients showed higher indices of disease activity at baseline (the mean serum TAP at entry was more than 4 times the normal upper limit), nearly 40% of them had skull involvement, and most patients were previously treated with bisphosphonates (91%); whereas in our series the baseline disease activity was lower (the mean serum TAP at entry was 2.7 times the normal upper limit), no patient had skull involvement, and fewer patients (51%) were previously treated with bisphosphonates. In fact, all these factors may influence the response to therapy (11, 13, 18, 21). Indeed, although in the present study non-significant differences were observed in the response to treatment when comparing previously treated and untreated patients, the percentage of normalization in serum TAP levels was slightly higher in the untreated group for both types of therapies. Thus, 81% and 87% of the patients treated with tiludronate and risedronate respectively, showed normalized serum TAP levels at 6 months

after the end of therapy when previously untreated, whereas these figures were 58% and 53%, respectively, in previously treated patients. Therefore, when comparing the effect of a single treatment in different studies, it is important to assess the baseline characteristics of the patients included in these studies. It should be noted that in the present study non-significant differences in clinical and biochemical parameters were observed between both groups of patients at inclusion. However, this study has several limitations. The absence of randomization and the small number of patients may limit our conclusions. Nevertheless, despite these limitations we believe the data are of interest, as they add information to the biochemical response of Paget's disease activity after the treatment with two different types of bisphosphonates.

In summary, the results of this study indicate that tiludronate and risedronate, given at the currently recommended dosages, induce similar decreases in Paget's disease activity during a one-year follow-up.

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