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ORIGINAL ARTICLE

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Scintigraphic, biochemical, and clinical response to zoledronic acid treatment in patients with Paget's disease of bone

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Abstract Bisphosphonates have long been used with success in the treatment of Paget's disease of bone (PDB). The aim of this study was to evaluate the early (up to 3 months) and late (at 12 months) scintigraphic, biochemical, and clinical response to a single intravenous infusion of zoledronic acid (ZOL) in patients with PDB serially assessed for 1 year. Nine patients with 30 bone lesions caused by PDB were prospectively evaluated. Total serum alkaline phosphatase (SAP) was serially measured. Scintigraphy was performed before and at 3 and 12 months after ZOL administration, and bone lesions were assessed quantitatively. After treatment, pain was alleviated in five of six patients starting from the first month. At 3 months, a significant decrease of SAP levels compared to baseline values was found (322 ± 211 IU/l before vs. 101 ± 36 IU/l 3 months after; $P < 0.05$), with normal values attained in all except one patient. The scintigraphic index of involvement (SII), a marker for the per-patient activity of the disease, was reduced from 14.4 ± 7.6 to 7.2 ± 1.8 ($P = 0.01$). The scintigraphic ratio (SR), a marker for the per-lesion activity of the disease, was reduced from 12.8 ± 7.7 to 7.0 ± 2.9 ($P < 0.001$). The values of markers of disease activity remained unchanged up to 12 months. A single intravenous administration of ZOL leads to a favorable clinical, biochemical, and scintigraphic response in patients with PDB starting as early as 3 months after treatment and lasting no less than 12 months (i.e., considerably longer than the other existing therapies).

Key words alkaline phosphatase · bisphosphonate · Paget's disease · scintigraphy · zoledronic acid

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Introduction

Paget's disease of bone (PDB) is a chronic disorder characterized by focal areas of excessive osteoclastic resorption coupled with secondary increased and disorganized osteoblastic activity resulting in abnormal bone formation and remodeling followed by deformity [1,2]. The prevalence of PDB is estimated to be between 0.5% and 8%, with the higher rates occurring in countries with populations predominantly of Anglo-Saxon extraction, whereas the lower rates are seen in the Mediterranean countries [3,4]. The diagnosis of PDB is primarily based on plain radiographs of painful areas, but bone scintigraphy is more efficient in assessing early lesions as well as the extent of skeletal involvement [2,5]. Measurement of total serum alkaline phosphatase (SAP) is a sensitive means for screening for PDB [2] and is effective in monitoring disease activity after therapeutic interventions [6].

The treatment of PDB aims at suppression of abnormal bone turnover, and for this aim bisphosphonates are the drugs of choice [5]. Bisphosphonates normalize biochemical markers of bone turnover, lead to replacement of chaotic woven bone with normal lamellar bone, and reduce bone pain [7]. Recently, the third-generation aminobisphosphonate, zoledronic acid (ZOL), has been introduced in the treatment of PDB [8–10]. Compared to other bisphosphonates ZOL has a higher affinity to bone mineral [11] and is a stronger inhibitor of the enzyme farnesyl diphosphate synthase, the major pharmacological target of these drugs [12]. ZOL administered as a single intravenous infusion, lasting no less than 15 min, ameliorates bone loss and bone strength [13] and produces more rapid, complete, and sustained response in PDB compared to daily administration of oral risedronate, without the gastrointestinal side effects of oral bisphosphonates [6,7,14]. ZOL also confers better compliance to treatment [6,7]. This form of therapy has only recently been introduced in the treatment of PDB; hence, little is known about the onset of its effect in the scintigraphic profile, biochemical markers, and pain relief.

To provide useful information in the management of PDB, this study evaluated early and late responses (up to 1 year) of clinical, biochemical, and scintigraphic parameters to a single intravenous infusion of ZOL in a group of patients with PDB serially assessed for 1 year.

Materials and methods

This was an open-labeled study with prospectively recruited patients with the diagnosis of PDB, satisfying the following criteria: (1) PDB documented by plain radiographs, bone scintigraphy, and increased SAP on two consecutive measurements; (2) presentation with either bone pain or skull or cervical vertebra involvement; (3) no recent fracture at a pagetic bone site; (4) no calcitonin or bisphosphonates treatment for at least 12 months before baseline assessment; (5) normocalcemia; (6) normal liver and kidney function tests; and (7) willingness to participate. All patients provided informed consent before enrollment, and the study protocol was approved by the local ethics committee. ZOL (5 mg) was administered as a single 30-min intravenous infusion. Patients received calcium carbonate (1500 mg) and vitamin D (400 IU) daily, as previously described [6,7], for 10 days before and 10 days after the infusion, until serum calcium was normalized.

Patients were asked for pain complaints in all follow-up visits, and the estimate of pain reduction was based on patient self-assessment in comparison to the severity of pain before the administration of ZOL.

Blood samples were obtained from each patient before treatment and after 1, 3, and 10 days, and also at 3, 6, and 12 months following ZOL infusion. Blood was drawn early in the morning after overnight fasting. Serum SAP, calcium, phosphorus, albumin, urea, and creatinine were measured within 1 h after venipuncture, using an automated immunoanalyzer (Olympus AU2700; Olympus, Hamburg, Germany). Serum was immediately recovered and frozen at –30°C for parathyroid hormone (PTH) measurements, using an automated immunochemiluminescent assay (Immulite 2000; DPC, Los Angeles, CA, USA).

All patients were submitted to bone scintigraphy before and at 3 and 12 months after the administration of ZOL. Spot images of the entire skeleton were acquired 3 h after intravenous injection of 740 MBq 99m-technetium-hydroxymethylene bisphosphonate, using a large field of view dual-headed gamma camera (AXIS; Philips, Cleveland, OH, USA), equipped with a general-purpose parallel hole collimator and interfaced to an Odyssey computing system. Energy discrimination was provided by a 20% window centered at the 140 keV photopeak, while the acquisition time was kept constant for all images of an individual patient. For the purpose of scintigraphic quantification, regions of interest (ROI) were drawn to encompass every individual bone lesion separately. For each patient, an unaffected ROI that served as a reference bony region was drawn in the middle of the left femur or, alternatively, the right femur, if the former was affected. Subsequently, the average counts per pixel in each pagetic ROI was divided by the average counts per pixel of the reference ROI to obtain the scintigraphic ratio (SR), a dimension-less indicator of disease activity in each individual lesion. A similar methodology has previously been used [15–17]. In addition, a second dimension-less index was introduced to provide an estimate of disease activity on a per-patient basis, in accordance with earlier works [15,18]; this was called the scintigraphic index of involvement (SII) and was defined as the sum of the products $f \times \mathrm{SR}$, where f represents the relative contribution of each lesion in the total area of pagetic involvement of the skeleton, as calculated from the area of the ROIs, and SR is the above-described scintigraphic ratio of the respective lesion. All ROIs in all bone scintigraphies (both at baseline and at follow-up imaging) were drawn by the same operator to minimize interobserver variability.

Plain radiographs of all bone lesions detected scintigraphically were obtained before and 1 year after ZOL administration and interpreted by an experienced radiologist, blinded to the other clinical, biochemical, and scintigraphic data.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or range and categorical data as numbers or proportions. The general linear model (GLM) was used in the analysis of variables with more than two repeated measurements to identify differences within the levels of the variable. Adjustment for violations of the sphericity assumption was performed with the Greenhouse–Geisser correction because of the small sample size. In case of significant differences, Tukey's post hoc analysis was used for multiple pairwise comparisons. Spearman's coefficient of correlation (r_s) was used to investigate for correlations between different variables. A P value less than 0.05 was considered statistically significant.

Results

Nine consecutive patients with PDB, five men and four postmenopausal women aged 62.6 ± 16.2 years, were prospectively enrolled in the study. Six of the patients had polyostotic and three had monostotic disease. In total, 30 pagetic lesions were identified by scintigraphy, and almost all of these were accompanied by findings on plain radiography at baseline assessment. Six patients had bone pain and three were asymptomatic. In the asymptomatic patients, ZOL was administered because of extensive skull lesions in two and involvement of the second cervical vertebra in one patient. Three patients received no therapy for PDB in the past, and the remaining six had not been treated with calcitonin or bisphosphonates for at least 12 months (range, 12–54) before baseline assessment. No patient had received ZOL in the past.

The biochemical and scintigraphic measurements during the monitoring period together with the statistically signifi-

Table 1. Biochemical and scintigraphic measurements of all study participants

	Baseline	Day 1	Day 3	Day 10	Month 3	Month 6	Month 12	*P* (GLM)	Reference range
SAP	322 ± 211	325 ± 203	281 ± 187	246 ± 160	101 ± 36*	91 ± 30*	93 ± 42*	0.011	30–120 IU/l
Calcium	2.43 ± 0.13	2.30 ± 0.13	2.18 ± 0.10*	2.35 ± 0.13**	2.33 ± 0.10	2.38 ± 0.08	2.38 ± 0.13	0.001	2.20–2.65 mmol/l
Phosphorus	1.23 ± 0.26	1.16 ± 0.29	0.94 ± 0.29	1.10 ± 0.26	1.13 ± 0.23	1.13 ± 0.19	1.16 ± 0.23	ns	0.81–1.45 mmol/l
Albumin	45 ± 3	43 ± 3	42 ± 3	45 ± 2	45 ± 2	46 ± 3	46 ± 2	ns	35–52 g/l
Urea	14.2 ± 5.0	13.7 ± 4.3	12.0 ± 2.9	13.0 ± 3.0	11.7 ± 3.6	12.8 ± 3.7	12.9 ± 4.2	ns	6.1–15.4 mmol/l
Creatinine	81 ± 17	90 ± 14	85 ± 19	79 ± 11	81 ± 19	80 ± 19	85 ± 17	ns	<106 µmol/l
PTH	6.8 ± 5.7				11.6 ± 8.7*	8.2 ± 5.6	7.5 ± 4.8***	0.030	0.8–5.8 pmol/l
SII	14.4 ± 7.6				7.2 ± 1.8*		5.5 ± 2.5*	0.001	

* $P < 0.05$ compared to baseline; ** $P < 0.05$ compared to the measurement at 3 days; *** $P < 0.05$ compared to the measurement at 3 months
GLM, general linear model; ns, not significant; SAP, serum alkaline phosphatase; PTH, parathyroid hormone; SII, scintigraphic index of involvement

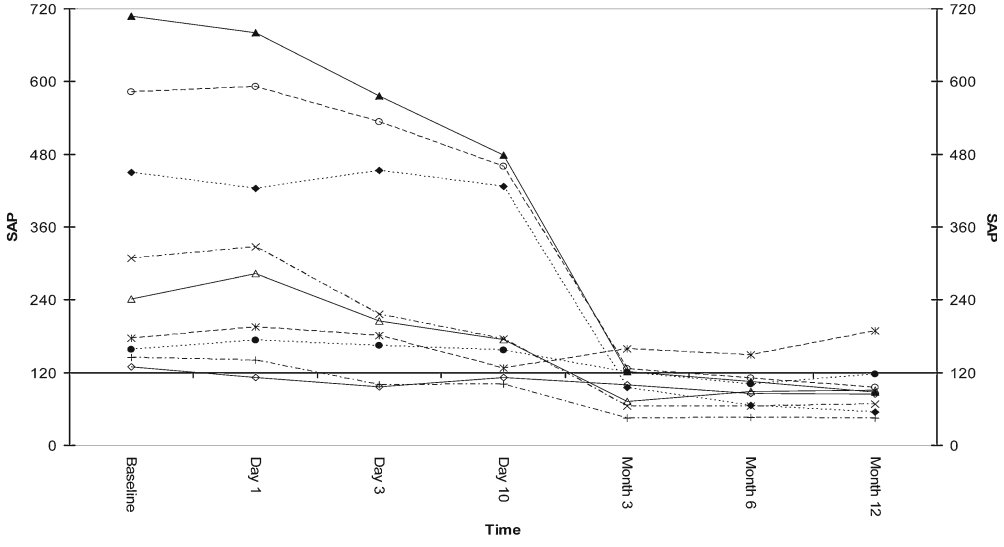

Fig. 1. Individual values of total serum alkaline phosphatase levels (*SAP*) throughout the study. Each patient is depicted by a separate *line*

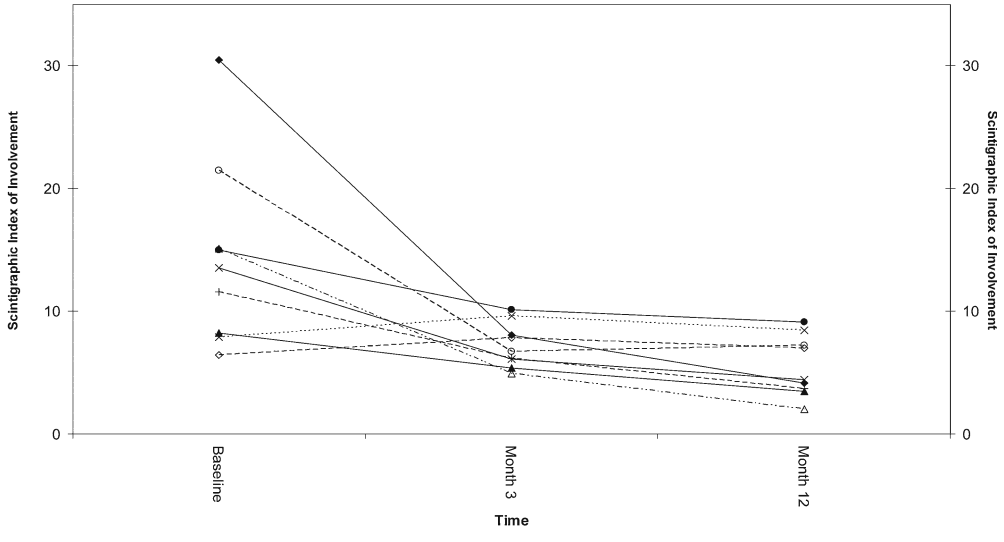

Fig. 2. Individual values of the scintigraphic index of involvement throughout the study period. Each *line* corresponds to a different patient

cant differences within and between each variable are summarized in Table 1. The values of SAP and SII in individual patients at the various time points are illustrated in Figs. 1 and 2, respectively.

At baseline, SAP was elevated in all patients (range, 129–708 IU/l) without gender differences. At 3 months, SAP was diminished in all patients by 57% (range, 10%–83%), independently of the baseline level, and was within normal limits in eight patients. SAP remained unchanged in those patients up to 12 months. There was a single patient with a low abnormal SAP value showing no response to treatment at any time point, both by SAP (Fig. 1) and by

Table 2. Individual scintigraphic lesions of all patients and their quantitative assessment during the study period

Patient	Location	SR at baseline	SR at 3 months	SR at 12 months
1	Skull	30.5	8.0	4.2
2	Left iliac	25.2	6.8	4.7
2	Right scapula	8.1	4.1	6.8
2	Skull	27.8	8.3	9.3
2	Left pubic	32.6	6.4	6.9
2	Left femur	3.3	2.1	3.4
3	Right iliac and pubic	13.5	6.1	4.4
4	Second cervical vertebra	11.9	5.6	2.2
4	Second thoracic vertebra	12.9	7.2	4.6
4	Right humerus	6.0	5.5	4.3
5	Left acromion	4.7	5.2	2.2
5	Right tibia	13.0	6.5	3.7
5	Skull	7.4	6.2	4.2
5	First–fourth lumbar vertebrae	10.1	6.0	4.4
5	Right iliac	6.5	2.9	2.2
5	Left iliac	5.8	2.9	2.1
6	Left iliac	9.5	6.8	5.7
6	Skull	15.9	12.6	10.7
6	Right patella	15.0	6.2	7.8
6	Left patella	13.4	6.4	7.8
6	Right iliac	17.0	8.7	8.0
7	Upper jaw	18.2	14.4	13.2
7	Nasal bone	20.4	13.9	11.4
7	Right acromion and clavicle	7.8	10.5	7.8
7	Left acromion and clavicle	7.5	8.0	5.4
7	Sacrum	6.7	8.7	8.3
8	Left public	6.0	7.7	7.5
8	Right humerus	8.4	9.6	8.7
8	Fourth lumbar vertebra	5.3	6.2	4.5
9	Left iliac	11.9	4.0	1.8

SR, scintigraphic ratio

scintigraphic measurements (Fig. 2). A significant decrease in the mean serum calcium of 10% (range, 4.3%–23.6%) in the third day was observed accompanied by a mild but not statistically significant hypophosphatemia (see Table 1). No clinical symptoms of hypocalcemia were observed, and calcium was normalized by the 10th day. PTH was significantly increased by 90% (range, 20%–252%) 3 months after ZOL infusion and returned to baseline levels at 12 months.

All scintigraphic bone lesions and their corresponding SR values at baseline assessment, at 3 and 12 months, are listed in Table 2. The baseline SR value of all lesions was 12.8 ± 7.7 and was reduced to 7.0 ± 2.9 ($P < 0.001$) at 3 months. There was a further but nonsignificant reduction to 5.8 ± 3.0 at 12 months. Regarding SII, in seven patients there was a 54% (range, 32%–74%) decrease at 3 months and a further decrease to 67% (range, 39%–86%) at 12 months. SII increased by 22% in both the remaining patients at 3 months and by 7% and 9% at 12 months (Fig. 2). In one of these patients, SAP was reduced at 3 months and in the other remained unchanged in follow-up measurements. Overall, both SR and SII diminished significantly 3 months after ZOL administration and remained unchanged at 12 months. Despite substantial scintigraphic improvement in most bone lesions, none of them had resolved completely at 12 months after treatment with ZOL. Serial bone scintigraphies of three different pagetic lesions are illustrated in Fig. 3.

No radiographic improvement was detected in patients at 12 months. The exception was a single male patient who had definite radiographic improvement of the pagetic lesion in the second cervical vertebra.

Four of six patients with painful bone sites at baseline assessment reported a significant decrease in the severity of pain in those locations at 10 days to 1 month after ZOL administration, and this improvement was maintained throughout the study period. One patient experienced an early decrease in severity of pain, which lasted for 3 months after ZOL administration, but pain gradually returned to its baseline intensity. One patient reported no difference in the severity of pain.

One day after ZOL administration three patients had a mild influenza-like illness presenting with musculoskeletal pain, headache, fatigue, and fever (up to 38.4°C in two patients), lasting 1–3 days. No serious adverse events occurred.

There were statistically significant correlations between SAP at baseline measurement and its degree of improvement at 3 ($r_s = 0.817$, $P = 0.007$), 6 ($r_s = 0.783$, $P = 0.013$), and 12 months ($r_s = 0.750$, $P = 0.020$). Similarly, there were statistically significant correlations between SII at baseline assessment and its magnitude of change at 3 ($r_s = 0.900$, $P = 0.001$) and 12 months ($r_s = 0.717$, $P = 0.030$). In addition, SR measurements followed a similar pattern ($r_s = 0.823$, $P < 0.001$ at 3 months and $r_s = 0.817$, $P < 0.001$ at 12 months).

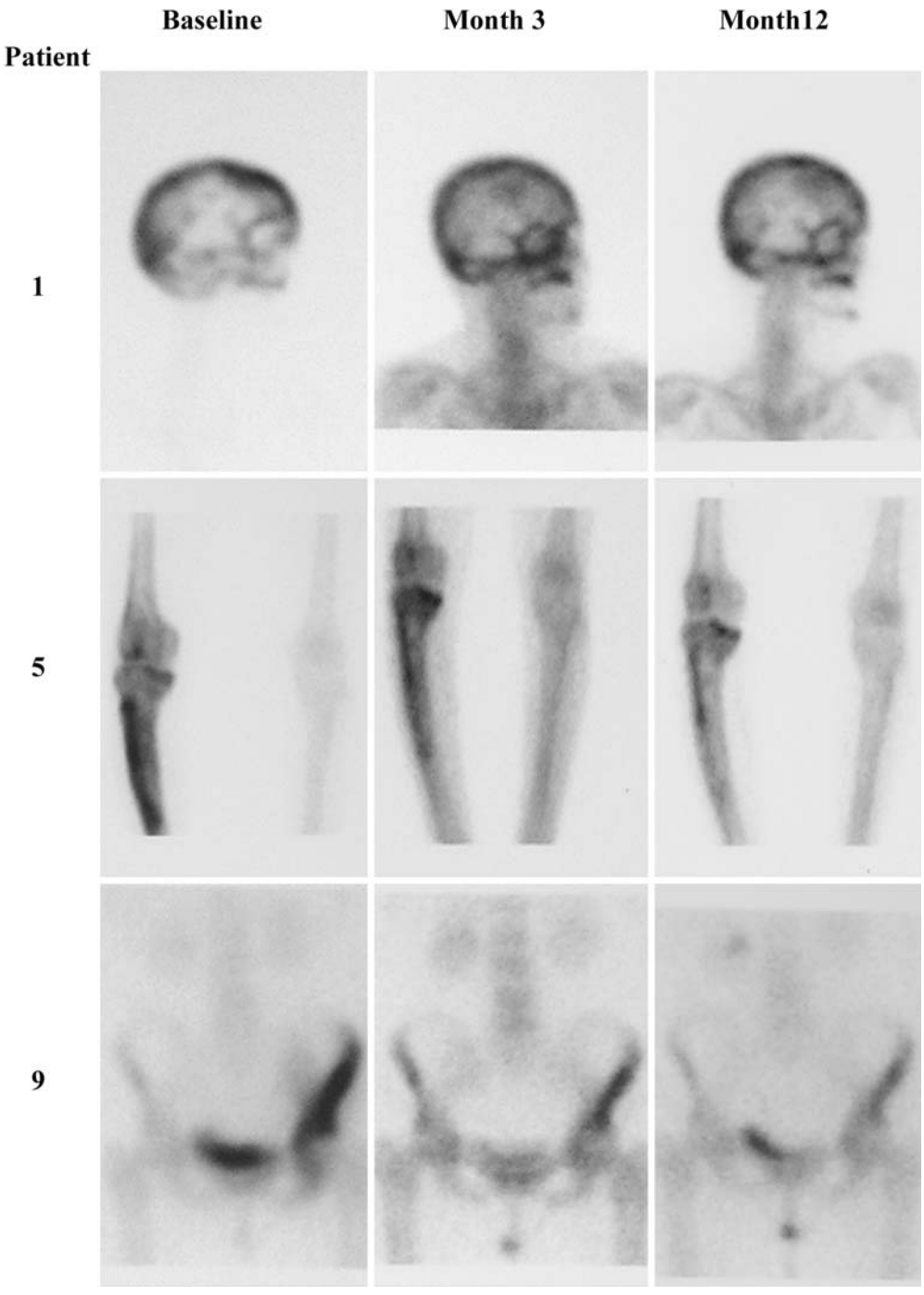

Fig. 3. Scintigraphic images of three bone lesions in three different patients treated with zoledronic acid. A progressive decrease in disease activity is shown between baseline imaging and follow-up scans

Discussion

This study demonstrates that a single intravenous ZOL infusion in patients with PDB results in a significant reduction in scintigraphic indices, besides the anticipated improvement in SAP measurements, as early as 3 months after treatment, and which lasts no less than 12 months, i.e., considerably longer than the existing other therapies. Pain was relieved in most patients, even before the onset of biochemical and scintigraphic changes. No serious adverse events were noted with this form of therapy.

Zoledronic acid is reported to be the most potent bisphosphonate to date [7–9,11,12], and the favorable scintigraphic, biochemical, and clinical changes at 3 months are consistent with this notion. To our knowledge, this is the first report of significant scintigraphic improvement as early as 3 months after a therapeutic intervention in PDB. Previous publications showed a decrease in radionuclide uptake in patients with PDB 6–12 months after treatment with

calcitonin [19,20], mithramycin [21], etidronate [22], pamidronate [17,23,24], or ibadronate [25]. On the other hand, none of the pagetic lesions of our patients resolved completely, which is in agreement with earlier data on serial pamidronate infusion in PDB [24].

It has been proposed that bone scintigraphy is the most sensitive way for assessing local disease activity [8], more sensitive than biochemical markers [25] and certainly more so than radiographs [26,27]. Scintigraphy has been shown to detect recurrence of PDB 6 months earlier than biochemical markers and clinical manifestations of the disease [17].

In routine clinical practice, apart from the usefulness of bone scintigraphy in the initial assessment of the disease, its potential role and the timing of imaging in the follow-up evaluation are debatable. However, in contrast to SAP, scintigraphy allowed an assessment of the response to treatment in individual lesions. Plain radiographs almost invariably could not detect bone changes, despite considerable scintigraphic and SAP improvement. Although neither bone scintigraphy nor radiographs alone can identify all lesions, scintigraphy is known to be a more sensitive technique in assessing the result of treatment in PDB [26,27].

SAP is a convenient indicator of treatment-induced changes in bone turnover because it is cheap, widely available, and has a low interassay variation [6]. In agreement with previous reports [7], SAP measurements 3 months after ZOL infusion showed a significant reduction compared to baseline values. SAP was normalized in all but one patient irrespective of the initial value and remained unchanged up to the end of the study period (see Table 1, Fig. 1). The general effect of ZOL on SAP change was proportional to its baseline value. Prolonged normalization of SAP has been reported after ZOL [6,14]. Our patients are being followed with no additional ZOL infusion at the end of the first year. ZOL maintains bone turnover within the reference range over 24 months from the initiation of the treatment, offering a longer remission rate than risedronate [6,14]. In contrast, SAP relapsed to pretreatment values 6 months after discontinuation of calcitonin [28].

In agreement with earlier data, PTH was elevated 3 months after treatment [7]. Transient secondary hyperparathyroidism developed after ZOL infusion as a compensatory mechanism to maintain normocalcemia. Calcium and vitamin D might have been administered for longer after achieving normocalcemia to shorten the duration of this transient secondary hyperparathyroidism.

One patient did not respond to ZOL treatment either by SAP or by scintigraphic criteria, with no obvious explanation for this lack of response. This patient was given, in the past, four different courses of alendronate or risedronate with no satisfactory therapeutic result. Resistance to treatment with etidronate or pamidronate has been described previously, but it is unclear if this applies to newer bisphosphonates [9,29]. It has also been reported that switching to a different bisphosphonate is usually effective [9,29]. Nevertheless, a recent study showed that ZOL infusion could achieve biochemical remission in most but not all patients with a previous unsuccessful therapy with pamidronate [30].

In two patients with polyostotic PDB, individual lesions responded differently to ZOL treatment (see Table 2), possibly because each lesion in a given patient with polyostotic disease has its own rate of turnover and thus a different susceptibility to the action of bisphosphonates. Previous data showed that bone turnover is a significant determinant of the amount of bisphosphonates retained within pagetic bone, and patients with high disease activity retain more bisphosphonates at skeletal locations with high turnover [31–34]. The significant correlations between baseline SAP, SII, and SR measurements and their respective degree of change in later assessments provide evidence supporting greater efficacy of ZOL treatment in cases of high bone turnover. Conversely, mild or no response to treatment was observed in cases with low abnormal values in markers of disease activity (Figs. 1, and 2).

Pain alleviation was noted in the majority of patients within 1 month after ZOL infusion. Previous series showed that biochemical changes after ZOL therapy were accompanied by pain relief and improvement in the quality of life [7,30]. Interestingly, in our study, there was one patient with a pretreatment borderline SAP value (129 IU/l; the upper limit being 120 IU/l) which was effectively suppressed (to 85 IU/l) after ZOL treatment. This patient showed clinical response (substantial reduction of pain) despite slight scintigraphic deterioration.

There were no serious adverse events, and transient influenza-like symptoms are well-recognized side effects of the treatment with intravenous amino-bisphosphonates [7,30]. A mild transient hypocalcemia developed despite calcium and vitamin D supplement before and after ZOL infusion.

In conclusion, a single intravenous administration of ZOL has no harmful side effects, and leads to a favorable clinical, biochemical, and scintigraphic response in patients with PDB as early as 3 months after treatment that lasts considerably longer than the existing other therapies (no less than 12 months). In the follow-up of certain patients scintigraphy, by virtue of its ability to discriminate local sites of response, could be used, along with SAP, to distinguish very early the nonresponders to therapy.

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