update article

Paget's Disease of Bone

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ABSTRACT

Paget's disease of bone is a focal disorder of bone remodeling accompanied initially by an increase in bone resorption, followed by a disorganized and excessive formation of bone, leading to pain, fractures and deformities. It exhibits a marked geographical variation in its prevalence. In Brazil it predominantly affects persons of European descent. The majority of the reported cases of the disease in Brazil are from Recife, owing to its peculiar mixed European colonization over approximately four centuries. The etiology is complex and involves both genetic and environmental factors. The disease is often asymptomatic and diagnosis is usually based on biochemical markers of bone turnover, radionuclide bone scan and radiological examination. Bisphosphonates, in particular zoledronic acid, are regarded as the treatment of choice for Paget's disease of bone. **(Arq Bras Endocrinol Metab 2006;50/4:814-822)**

Keywords: Paget's disease of bone; Prevalence; Bone resorption; Bisphosphonate; Calcitonin

RESUMO

Doença de Paget Óssea.
Doença de Paget óssea é uma desordem focal da remodelação óssea, inicialmente acompanhada de um aumento da reabsorção óssea, seguida de desorganizada e excessiva formação óssea, levando a dor, deformidades e fraturas. Exibe uma variável distribuição geográfica em sua prevalência. No Brasil acomete predominantemente pacientes de descendência européia. Recife, devido à sua peculiar colonização mista européia por cerca de 4 séculos, tem a maioria dos casos relatados no Brasil. A etiologia é complexa e envolve fatores ambientais e genéticos. A doença é freqüentemente assintomática e o diagnóstico é feito usualmente através dos marcadores bioquímicos do *turnover* ósseo associado a cintilografia óssea e dos sinais típicos do exame radiológico. Os bisfosfonatos representam o tratamento de escolha na doença de Paget óssea, particularmente o ácido zolidrônico. **(Arq Bras Endocrinol Metab 2006;50/4:814-822)**

Descritores: Doença de Paget óssea; Prevalência; Reabsorção óssea; Bisfosfonato; Calcitonina

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PAGET'S DISEASE OF BONE (PDB) was first described in 1876 by Sir James Paget (1). It is a focal, progressive disorder of bone remodeling (2). Initially, there is an excessive osteoclastic bone resorption, followed by a secondary increase in osteoblastic activity resulting in a mosaic pattern of lamellar bone. Normal bone is replaced by a disorganized, hypertrophic and softened osseous structure that is prone to deformity and fracture. Other pathologic features include an excess of fibrous connective tissue in

the marrow spaces and a marked increase in blood vessels. The main sites affected are the vertebrae, long bones, pelvis and skull (3).

EPIDEMIOLOGY

In countries where the disease is prevalent, up to 3% of the population over the age of 40 are affected. It is common in England, the United States, Australia and New Zealand and rare in Scandinavia, Asia and Africa. Recent studies from England, New Zealand and the USA have shown that there has been a decrease in the prevalence and severity of Paget's disease of bone (PDB) (4,5).

The frequency of PDB in most of South America is low (6-8). However, a number of cases have been reported in Argentina and Brazil. Two large series of patients have been published in Buenos Aires (9).

In Brazil the disease predominantly affects patients of European descent (10). Recife, due to its peculiar mixed European colonization over about 4 centuries, has the majority of reported cases of PDB in Brazil for a reason dating back to Dutch rule in the Recife area during the seventeenth century. Amsterdam was a place of great religious tolerance at a time of anti-semitism, which is why Jews from many European countries moved to that part of the continent and then to the new colony in Brazil (11). Moreover, most Portuguese who moved to the Recife area during the Dutch period were in fact European Jews who had converted to Christianity in an attempt to escape the Inquisition, and found a new and tolerant environment as a result of the religious policy adopted by the Dutch in Pernambuco, where the first synagogue in the Americas was built. This is very different from the rest of Brazil, where migration at that time was of truly Portuguese origin. In fact only small series of cases of PDB have been reported from other parts of Brazil (12,13). A recent publication involving 103 cases of PDB at a reference center in the city of Recife (14) reveals that most cases occurred in patients of European descent. Five of the patients were black, four were of mixed Portuguese and Indian blood, six were second generation Jews of Ucranian origin, while thirteen were of Italian, three of English, two of French and fifty-eight of Portuguese and Dutch descent, and seven of uncertain origin. Although the etiology of PDB is unknown, the disease may be caused by genetic factors and/or slow virus infection. A family history is present in about 15% of the patients and first-degree relatives of the patients have a sevenfold increase in risk of developing the disease (15,16). Several susceptibility loci have been linked to the disease, including SQSTM1 (encoding sequestosome 1 or p62) on chromosome 5q35 and TNFRSF11A (encoding RANK) on chromosome 18q21-22. The SQSTM1, also known as p-62 or sequestosome 1, is located on chromosome 5q35 and is a signaling protein that appears to be involved in the pathogenic mechanisms as it increases osteoclast activity. Chance mutations (P392L) of this gene have been detected in over 30% of familial PDB (17).

The role of SQSTM1/ p62 has not yet been fully clarified. There is evidence that the mutations may reduce the ability to sequester cytoplasmatic proteins, lead to changes in the nuclear factor kB (NF-kB) and result in increased osteoclastogenesis. The action of osteoprotogerin on the RANK receptor has also been described (18,19). Biological (hybridization in situ and immunohistochemistry) studies have suggested the possibility of infection of the osteoclasts by a virus, particularly the paramixovirus, as the causation of PDB, but this virus has yet to be isolated (20-22) and some viral components have been detected as nuclear inclusions in the osteoclasts of affected patients. These correspond to measles virus nucleocapsid protein and respiratory syncial virus, and more recently the full-length sequence for the measles virus nucleocapisid gene in bone marrow was obtained from patients with PDB.

CLINICAL AND RADIOLOGICAL PRESENTATION

In the 103 patients of our cohort (14), the female/male ratio was 1.2:1, and ages ranged from 48 to 86 years. Forty patients presented with monostotic (27 women and 13 men, aged 70.3 ± 6.8 years), and sixty-three with polyostotic disease (29 women and 34 men, aged 65.8 ± 9.6 years). Most patients presented with symptoms (almost 50% with joint or bone pain), and 36% were asymptomatic (table 1). This suggests that our Institutional prevalence, as a reference center, may be underestimating the true prevalence in the general population, even with the use of biochemical screening.

Regarding ethnic background, five patients were black, four had native Indian with Portuguese ancestry, six were part of the second generation of European Jews from Ukraine, thirteen were of Italian descent, three were of English descent, two were of French descent, fifty-eight had a clear Portuguese and

Table 1. Age, gender and clinical presentation of 103 patients with Paget's Disease of Bone.

	Monostotic	Polyostotic
No. of patients	40	63
Gender (M/F)	13/27	34/29
Age (yr)	70.3 or 6.8	65.8 or 9.6
Presentation		
Asymptomatic	17	10
Pain	19	31
Deformity	3	9
Pain + deformity	1	12
Fracture	1	2
Deafness		4

Dutch ancestry, and seven had an uncertain ancestry. Blue eyes were present in 19 patients (18.5%) and a family history in 8 (7.8%).

Paget's disease of bone is usually asymptomatic. In most cases it is detected accidentally through radiological findings or by the serum increase in alkaline phosphatase while other clinical conditions are being investigated (23). Pain and deformity are the most common presentations. The pain arises from the pagetic lesion itself or, more frequently, from indirect complications such as degenerative arthritis, nervous compression or osteosarcoma. Other major causes of pain are increased vascularization, distortions of the periosteum resulting from the disorganization of bone remodeling and focal mechanical traumas (24). Hypertrophy of bone in the subchondral region may damage the cartilage, leading to osteoarthritis. Distinguishing pain of pagetic origin from that resulting from osteoarthritis is difficult. A response to the specific treatment for PDB may clarify this question.

The deformity affects mainly the long bones, skull and clavicles.

Pathological and/or traumatic fractures may arise as a result of pagetic lesions and the fissures may be complete or incomplete. Fractures of the femur occur more frequently than those of the tibia.

Diagnosis is mostly determined by radiography, the widening of bone being the most visible radiological feature. Other radiological findings include thickening of the cortex, osteolytic areas and osteosclerosis (25).

Lytic lesions arise in the initial phase and may acquire a focal aspect (osteoporosis circunscriptis) or a candle flame appearance. Next, areas of sclerosis appear, leading to the mixed aspect of lytic and sclerotic areas. The radiological findings are usually characteristic, but occasionally a differential diagnosis needs to be made with lytic or sclerotic metastases. The radionuclide bone scan is the most sensitive test in identifying PDB lesions, but is not specific and should be followed by plain X-rays. It is recommended that a bone scan be performed in all patients as part of the initial investigation. This procedure is intended to determine the distribution of the disease, identifying the sites affected and determining their potential for developing complications.

From our cohort the skeletal involvement was as follows: vertebrae: 38 patients (37%), long bones of the lower extremities: 37 patients (36%) and of the upper extremities: 8 patients (7.8%), pelvis: 64 patients (62%), skull 29 patients (28%), scapula: 5 patients (4.8%), clavicle: 3 patients (2.9%), metacarpals: 2 patients (2%) sternum: 2 patients (1.9%), and ribs: 1 patient (figure 1). Figures 2 and 3 show the percentage of patients according to sites of skeletal involvement with respect to monostotic or polyostotic presentation. More patients in the polyostotic group had involvement of pelvis, skull and vertebrae (56 versus 16, 20 versus 9, and 45 versus 4 respectively). Also infrequently affected sites like hands, scapula, clavicle and ribs were also seen more often in the polyostotic than in the monostotic presentation.

LABORATORY FEATURES AND MONITORING

In the biochemical evaluation of PDB the markers of bone remodeling are extremely useful. Clinically, the one most commonly used is serum alkaline phosphatase. This marker, however, may be normal in around 10% of patients, as well as being subject to metabolic interference in patients with liver disease. In these cases, bone specific alkaline phosphatase or urinary markers of bone resorption may be helpful (26).

Markers such as C-Telopeptide (CTX) and N-telopeptide (NTX) have been employed. Telopeptides are type I collagen degradation products and may be measured by immunoassays, reflecting the degree of bone resorption. They are used as markers of the activity of the disease and in the assessment of the response to therapy. In the terminal C telopeptides the α-aspartic acid present is converted to the β form of aspartic acid as the bone ages. This may be measured in human serum using monoclonal antibodies that recognize all the fragments of type I collagen that contain the β-8A octapeptide in duplicate (sβ-CTX) (27).

It has been postulated that the pagetic bone matrix decreases the degree of β-isomerization of C-

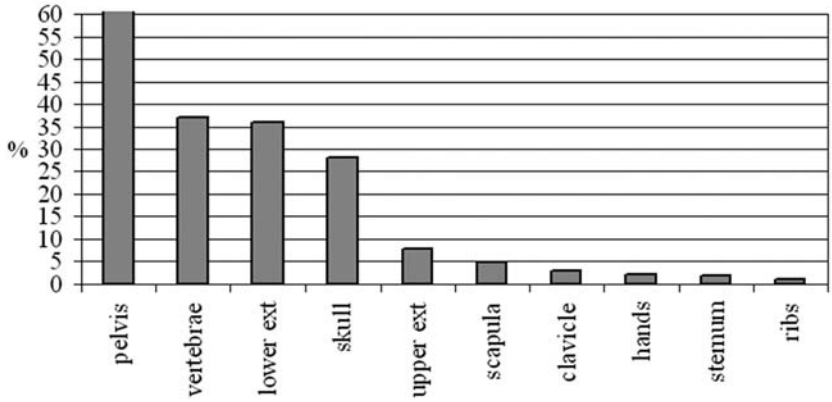

Figure 1. Skeletal involvement in 103 patients with Paget's Disease of Bone.

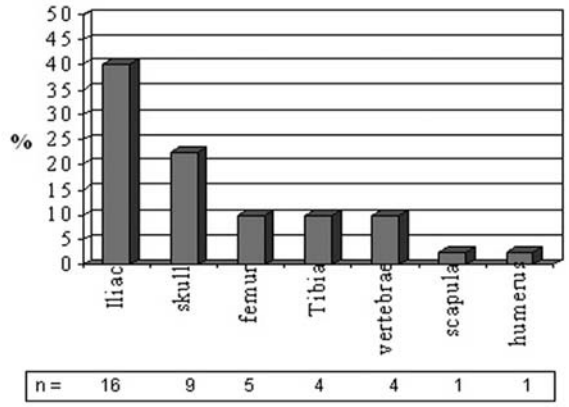

Figure 2. Skeletal involvement in 40 patients with monostotic disease.

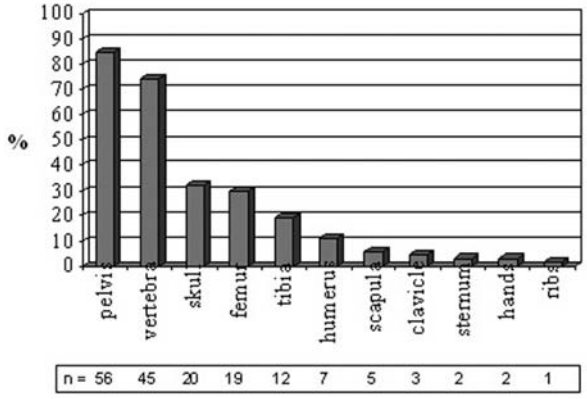

Figure 3. Skeletal involvement in 63 patients with polyostotic disease.

terminal telopeptide, and some studies have demonstrated that the urinary excretion of non-isomerized forms (α-CTX) and urinary NTX, which may not be isomerized, are better predictors of disease activity than serum alkaline phosphate and urinary β-CTX (27,28). Also, anti-β-CTX antibodies tend to react more intensively with normal bone while the pagetic woven bone tends to stain predominately with anti α-CTX antibodies (29).

However, by using newer techniques for measurements of β-CTX in serum by electrochemoluminescence, it is possible to detect disease activity in those patients with normal serum AP. Pyridinoline and deoxypyridinoline, also employed as markers of bone remodeling, constitute the cross-links of the helicoidal structure of type 1 collagen whose concentration in the urine is proportional to the activity of the osteoclasts. Deoxipiridinoline is more sensitive than piridinoline.

In our study conducted at the Pernambuco Osteoporosis Center, serum alkaline phosphatase (AP) remains the most practical tool to evaluate and monitor disease activity in pagetic patients and is elevated in the majority of them. In the monostotic/polyostotic patients, serum AP was 2.2 ± 1.9 / 5.9 ± 2.8 (mean ± SD) times the upper limit of normal respectively. Eight patients had normal serum AP activity (seven had high urinary N-terminal-telopeptide [NTX] levels, and one had high serum β-isomerized C-terminal-telopeptide levels [β-CTX]). Ten patients had their urinary NTX measured, and 15 patients had their serum β-CTX measured. All of them showed values above 95º centile for normal individuals (figure 4 and 5).

COMPLICATIONS

The most frequent complications include the following: pathological fractures, bone deformities, degenerative arthritis, loss of hearing, basilar invagination, nerve root or cord compression, and rarely hypercalcemia during immobilization, increased cardiac output in cases with severe bone involvement and osteosarco-

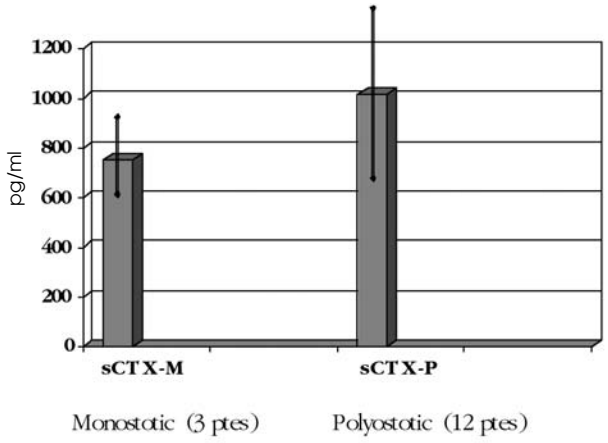

Figure 4. Serum β-CTX in 15 patients with Paget's Disease of Bone. Reference range for premenopausal women: 80–450 pg/ml.

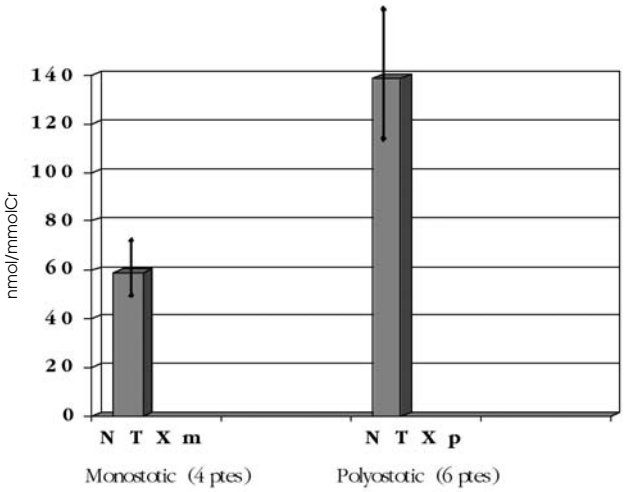

Figure 5. Urinary NTX in 10 patients with Paget's disease of bone. Reference range for premenopausal women: 5–53 nmol/mmolCr.

ma, the latter being a rare complication that occurs in only 0.7–1% of the cases (30). Deafness may be of the conduction type, owing to the involvement of the ossicles of the middle ear, of central origin, from compression of the auditory nerve, or a mixed form.

Calcium and phosphate in the blood are normal in the majority of patients with PDB. Nevertheless, hypercalcemia may occur as a result of prolonged immobilization. Primary hyperparathyroidism has been reported in patients with PDB, but it is unclear whether there is any relation between these two diseases, and compensatory secondary hyperparathyroidism may also occur.

TREATMENT

The purpose of treatment is to restore normal bone metabolism, relieve bone pain and prevent future complications, particularly deformities of bone, secondary osteoarthritis, fracture and compression of nerve structures, prepare for orthopedic surgery to reduce bleeding and control hypercalcemia due to immobilization.

Calcitonin was the first osteoclast inhibitor to be used and nowadays represents the second treatment option in PDB. It suppresses bone turnover and alleviates bone pain, but is more expensive, less effective, and causes more side effects than the bisphosphonates. It is given in an initial daily subcutaneous dose of 100 U for 3–6 months, after which the dose should be reduced (31). The normalization of alkaline phosphatase is unusual and only occurs in patients with a small increase in bone turnover. The suppression of disease activity does not persist for very long, even with the continuation of the drug. Antibodies develop in around 30–60% of the patients (32,33). Side effects occur in approximately 10% of the patients and include nauseas, a metallic taste and flushing.

The bisphosphonates represent the treatment of choice in PDB. They are pyrosphosphate analogues, whose oxygen bridge is replaced by a carbonate bound to several lateral chains. Their characteristic bindings of phosphorate-carbon-phosphorate (P-C-P) make them resistant to the hydrolysis of the phosphatases, allowing them to bind to the calcified bone matrix. They bind to the bone surfaces, preferably in areas of high bone turnover. When taken orally, they are poorly absorbed, ranging from 0.5 to 3%, especially in the presence of food or even of small amounts of calcium salts. For this reason they should be administered on an empty stomach. They may produce side effects in the upper gastrointestinal tract, such as heartburn, dyspepsia and esophageal ulcers, and caution should be exercised in administering them to patients with duodenitis and gastritis. They are contraindicated in those suffering from esophageal disease. Other side effects that may occur are acute febrile reaction and, more rarely, uveitis and rash. Rare occurrences of osteonecrosis of the mandible and maxilla have been reported in patients receiving new generation of bisphosphonates (34,35). Most osteonecrosis cases have occurred in cancer patients. No cases were reported with zolidronic acid in the treatment of Paget's disease. The first-generation bisphosphonates, such as

etidronate, are weak antiresorptives, while the second and third generation ones, which contain nitrogen in their molecules (amino bisphosphonates) are much more powerful. They inhibit farnesil pyrophosphatase synthase, an enzyme essential for the prenilation of small G proteins along the cholesterol synthesis pathway which, when inhibited, triggers failure of the resorptive function, leading to cell death (36).

The first bisphosphonate to be used in PDB was etidronate. New, more potent biphosphonates have proved to be more effective, leading to more prolonged periods of remission. Etidronate was used for the first time in the treatment of PDB in 1971 (37). The recommended dose is 5 mg/kg/day (average dose 400 mg/day) for 6 months (37,38). In general, patients whose disease is very active show a moderate clinical and biochemical improvement and a rapid relapse after the medication is suspended, tending to become more resistant after a repeated course of therapy. Histological studies of bone have shown osteomalacia in both pagetic and nonpagetic bone following treatment with 10–20 mg/day per day, but not with a dose of 5 mg/day (39,40).

Pamidronate is 10 to 100 times more potent than etidronate and produces a reduction of bone remodeling in 60–70% of patients (41,42). It is used parenterally in a single IV infusion of 60 mg in cases in which there is little disease activity (alkaline phosphatase 2–3 times above the normal maximum value). Larger doses (90–180 mg), which may be given for three or four days, may be preferable in patients with more pronounced disease activity (43). The maximum dose given in a single day is 90 mg, diluted in a saline or glucose solution for 4–6 hours.

Oral alendronate is more effective than etidronate in the treatment of PDB. It may be used in a dose of 20–40 mg/day for 6 months (44). In a dose of 40 mg/day for 6 months it leads to a 77% decrease in alkaline phosphatase, compared with the 44% decrease produced by etidronate (45). The normalization of alkaline phosphatase is also more frequent in patients treated with alendronate than in those treated with etidronate (63.4% vs. 17%).

Tiludronate is recommended in a dose of 400 mg/day for 3 months, normalizing alkaline phosphatase in 35% of patients (46). It is more effective than etidronate and does not cause demineralization of bone (47).

Clodronate is more potent than etidronate and does not lead to defects of mineralization. It should be given intravenously in a daily dose of 300 mg for 5 days (48), but is usually less effective than pamidronate.

Risedronate in a daily dose of 30 mg for 2 months leads to the normalization of alkaline phosphatase in 73% of patients, compared with a 15% decrease in those on a daily dose of 400 mg of etidronate for 6 months. Sixteen months after the cessation of medication, 53% of the patients on risedronate remain in remission, compared with 14% of those on etidronate (49). In one study patients with resistance to calcitonin and pamidronate, associated with severe bone involvement, risedronate caused a significant reduction in the levels of serum alkaline phosphatase (50).

Ibandronate is another bisphosphonate that has also been used safely and efficaciously in PDB in an intravenous dose of 2 mg (51).

Zoledronic acid, also known as zoledronate, is 10,000 times more potent than etidronate and 100 times more potent than pamidronate (52). It is used intravenously for 15–20 minutes. Patients with resistance to other bisphosphonates usually respond to zoledronic acid (53), which is highly effective in reducing the biochemical markers of bone remodeling (54).

Zoledronic acid may lead to more rapid and prolonged remission in the treatment of PDB than risedronate (55). When evaluated for 6 months after a single 5 mg infusion for 15 minutes, resulting in the normalization of alkaline phosphatase or in a fall of at least 75%, it leads to a 96% decrease in alkaline phosphatase, compared with a 74.3% decrease with a daily 30 mg dose of risedronate for 3 months. More patients in the zoledronic acid group achieved normal alkakine phosphotase than those in the risedronate group (88.6% vs. 57.9%).

All patients treated with bisphosphonates should be given a calcium and vitamin D supplement.

Table 2 shows the initial therapeutic responses with calcitonin and the most commonly used bisphosphonates in a group of patients from our cohort. The fall in serum AP, after a median follow-up of 6 months, was as follows: 51.8 ± 15% with oral etidronate, 61.2 ± 8.4% with oral alendronate, 76.2 ± 5.1% with intravenous pamidronate, 78.2 ± 4.0 with oral risedronate, and 85.0 ± 3.9% with intravenous zoledronic acid.

A surgical procedure is indicated in certain situations, such as a hip replacement, severe osteoarthritis, osteotomy for the correction of a deformed tibia, occipital craniotomy for decompression of the posterior fossa in patients with platybasia and for the decompression of nerves.

Patients due to undergo elective surgery should be treated preoperatively with an intravenous infusion of a bisphosphonate such as pamidronate or zoledro-

Table 2. Initial (6 months) therapeutic responses in 77 patients with Paget's Disease of Bone. Three patients were treated with SC, with 37% fall in AP. One patient was treated with IV Clodronate, with 60% fall in AP.

Agent (Initial treatment)	Monostotic (No. of patients)	Polyostotic (No. of patients)	Fall in AP (% mean ± SD)	Normal AP
Etidronate (oral)	9	12	51.8 ± 15.2	45%
Alendronate (oral)	14	11	61.2 ± 8.4	65%
Pamidronate (IV)	1	13	76.2 ± 5.1	70%
Risedronate (oral)	1	3	78.2 ± 4.0	70%
Zolendronate* (IV)	1	8	85.0 ± 3.9	96%

Normal AP: normalization of AP following treatment.
* Single IV infusion of 4 mg

nic acid in order to decrease hypervascularity, thereby reducing bleeding during surgery.

Regarding the control of pain, when the pain is directly attributable to PDB, it is usually relieved by antiresorptive treatment (bisphosphonate or calcitonin). When pain is the result of bone deformity or secondary osteoarthritis, acetominofen, nonsteroid anti-inflammatories or cox-2 inhibitors may be of use.

FOLLOW-UP

The patient is considered to be in remission when the normal levels of biochemical markers, such as alkaline phosphatase, have been reached and in partial remission when there is a fall of over 75% three to six months after the start of treatment. Alkaline phosphatase should be measured every four to six months after the course of therapy and a new treatment should be given if the alkaline phosphatase is above normal or above the previous lowest value. Bone resorption markers such as C-telopeptide exhibit a high sensitivity, especially in individuals with normal alkaline phosphatase (56).

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