The Use of Intravenous Aminobisphosphonates for the Treatment of Paget's Disease of Bone

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Abstract: Paget's disease of bone is a focal skeletal disorder characterized by the formation of structurally abnormal bone, deformity and other complications leading to significant disability and bone pain. Recently, the availability of newer, more potent nitrogen-containing bisphosphonates has improved treatment outcomes, allowing a more effective and convenient management of this disorder.

Key Words: Paget's disease of bone, bone turnover, bisphosphonates, zoledronic acid, pamidronate, neridronate.

1. INTRODUCTION

Paget's disease of bone (PDB) is a chronic disorder which typically results in enlarged and deformed bones in one or more regions of the skeleton [1, 2]. Excessive bone breakdown and formation can cause the bone to weaken. As a result, bone pain, arthritis, bone deformities and fractures can occur. This disorder is most common in white people of European descent with a slight predominance in males, but it also occurs in blacks, whereas it is rare in people of Asian descent [3-5]. Clinical, radiological, and necropsy data from different countries suggests pronounced geographical variations in the prevalence of the disease, with highest prevalence rates in Britain, and other countries with high rates of immigration of people of British descent in the 19th and 20th centuries [3, 5]. A recent UK study in large cohort from the General Practice Research Database over the period 1988–1999 indicated an incidence rate of clinically diagnosed PDB of 5 per 10,000 person-years among men and 3 per 10,000 person-years among women 75 years of age [6]. Several studies suggested declining rates in both the prevalence and severity of PDB [7-9]. It is important to emphasize the localized nature of Paget's disease. It may be *monostotic*, affecting only a single bone or a proportion of a bone, or may be *polyostotic*, involving two or more bones. Sites of disease are often asymmetric. Although progression of disease within a given bone may occur, the sudden appearance of new sites of involvement some years after the initial diagnosis is uncommon.

The characteristic feature of the disease is an increased bone resorption followed by an increase in bone formation. It is generally believed that the primary cellular abnormality in PDB is in the osteoclasts, while the osteoblasts are intrinsically normal [10], even though this is not proven conclusively [11]. Pagetic osteoclasts are markedly increased in number as well in size and contain up to 100 nuclei per cell [10, 12]. Moreover, pagetic osteoclasts precursors are hyperresponsive to 1,25-dihydroxy-vitamin D and produce increased amounts of interleukin 6 [10, 13]. The marrow microenvironment also appears to be abnormal and has an enhanced capacity to induce osteoclast formation compared with the normal marrow microenvironment [13, 14]. It has been discovered that levels of RANK ligand mRNA, a potent stimulator of osteoclast formation which may be the common mediator for the effects of several osteoclastogenic factors on osteoclast formation [15] are significantly elevated in the stromal cell line derived from patients with PDB compared to that from controls [10, 13]. Generally the evolution of the disease follows three major phases. In the early phase, termed "*osteolytic phase*" bone resorption predominates and there is a concomitant increased vascularity of affected bones. Commonly the excessive resorption of pagetic bone by osteoclasts is followed closely by formation of new bone by osteoblasts. During this second phase of the disease the new bone that is made is structurally abnormal, presumably because of the accelerated nature of the remodeling process. Newly deposed collagen fibers are laid down in a disorganized rather than a linear fashion, creating the so called "*woven bone*". Such a woven-pattern is not specific for PDB but it just reflect a high rate of bone turnover. With the time, the hypercellularity at the affected bone may diminish leading to development of a sclerotic, less vascular, pagetic mosaic without evidence of active bone turnover. This is the so-called "sclerotic" or "burned-out" phase of PDB. Typically all these three phases of the disease can be seen at the same time at different sites in a single pagetic patient.

Pain, and namely localized bone pain, is the most common symptom that brings a patient with PDB to a physician. Pain varies greatly from patient to patient depending on the location and extent of the disease. It may arise from increased vascularity, from distortion of the periosteum due to disorganized remodeling, or from a focus of mechanical stress. Alternatively, another source of pain may be from

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irritation of nerves covering affected bones. However, many patients who have PDB do not know they have it, since the disease may be so mild that is not detected. Moreover, the patient's symptoms are often confused with arthritis or other skeletal disorders. Sometimes, the patient's doctor is alerted to the possibility of PDB when physical deformities appears (i.e. enlargement of the skull or bowing of the tibia) or when a blood test reveals an elevated level of bone turnover markers. Among the various markers, total or bone specific alkaline phosphatase have a good diagnostic accuracy as a measure of increased bone remodeling of pagetic bone and are commonly used for diagnosis as well as for monitoring the response to treatment [16]. However, especially in extensive and active disease, most markers of bone turnover will be abnormal and the choice can then be based on cost and availability.

In most cases, the diagnosis of PDB is made only after complications have developed. These complications mainly include osteoarthritis, fractures, severe bone deformity, neurological syndromes and osteosarcoma, which significantly affect the morbidity and reduce the quality of life of patients [17-23]. Osteoarthritis is common, affecting up to 50% of patients with PDB and can be quite painful [6, 17]. A variety of disturbances and neurological syndromes can be associated with PDB of the skull and spinal column as result of pressure on the brain, spinal cord or nerves by enlarged pagetic bones [18]. Irreversible hearing loss can occur in 13% of patients [19]. Skull deformity may result in enlargement of the vault, with a characteristic appearance particularly of the forehead (*frontal bossing*) or of the maxilla (*leontiasis osseum*). Bowing of weight bearing bones is another common feature of PDB [19]. It occurs most commonly in the femur, tibia, and humerus. These type of deformities are often associated with stress fractures on the convex surface of the bowed bone. Pathologic fractures may occur at any stage even though are more common in the lytic phase of the disease. Blood flow may be markedly increased in extremities involved with PDB, leading in some instances to high-output heart failure. There are also reports suggesting an increased incidence of calcific aortic disease or other valve calcifications [6, 17, 21]. One of the most serious complications is neoplastic degeneration of pagetic bone with an increased incidence of sarcomas, expecially in polyostotic cases of the disease. Approximately 0.5-1% of pagetic patients develop osteosarcoma, an increase in the risk that is several thousand-fold higher than in the general population. It has been estimated that 20% of the patients with osteosarcoma over the age of 60 have PDB as a predisposing condition [22]. The sarcomas most frequently arise in the femur, tibia, humerus, skull, mandibula, and pelvis while rarely occur in vertebrae. Death from massive local extension or from pulmonary metastases occurs in the majority of cases in 1 to 3 years. Benign giant-cell tumor also may occur in pagetic bone [23]. Radiographic evaluation of lesion as well as bone biopsy may be useful for diagnosis.

The cause of PDB remains in large part unknown and is currently an area of intensive investigation. Both genetic and non-genetic factors have been implicated in the pathogenesis of this disease [10]. Some studies described the presence of paramyxoviral gene products in pagetic osteoclasts, suggesting that the disorder may be caused by a slow-acting viral infection of bone, (a condition which is present for many years before symptoms appear). There are also data supporting a hereditary hypothesis, since the disease may appear in more than one member of a family, and mutations in different genes have been recently associated with classical PDB or PDB-related disorders. In particular, mutations in the *SQSTM1* gene encoding sequestosome 1, have been described in a consistent number of sporadic and familial PDB patients [10]. How the virus and the genetic factors are intertwined in PDB pathogenesis is not yet clear. Genetic factors may increase an individual's chance of getting the disease. Another explanation is that the genetic version of the disease represents only one group of PDB patients and that the other patients have a type of PDB that requires viral exposure.

2. TREATMENT OPTIONS FOR PAGET'S DISEASE OF BONE

2.1. Indications for Treatment

The primary goal of PDB treatment is to restore normal bone turnover in order to relieve symptoms such as bone pain and prevent complications that result from the abnormal resorption and overgrowth of pagetic bone. Treatment can be also indicated for patients with orthopedic complications, undergoing elective surgery at affected bone sites. In this case the normalization of bone turnover is able to reduce blood flow in pagetic bone and thus decrease blood loss during surgery. In elderly polyostotic patients with advanced disease, treatment is also indicated for the management of hypercalcemia arising from immobilization. However, almost any PDB patient (particularly those with the involvement of the skull, weight bearing bones, and bones adjacent to major joints) may benefit from antiresorptive treatment, even if there are no symptoms, because of the potential to reduce disease progression, bone deformity and related complications. Indeed, even though it has not been proven conclusively that restoring normal bone turnover effectively reduces the risk of later complications, in untreated PDB the progression of disease usually occurs with extension of osteolitytic changes and bone deformity [24]. Conversely, suppression of bone turnover with antiresorptive therapy is associated with normal lamellar patterns of new bone deposition, as seen on bone biopsy specimens [25], and there are isolated case reports showing improvement of deformity or hearing loss after treatment [26, 27]. A long-term preliminary observation of 41 PDB patients who received multiple bisphosphonate courses for an average of 12 years evidenced an increased prevalence of complications in patients whose bone turnover marker levels were lowered but not normalized [25].

Since in PDB the increased rate of osteoclast resorption of bone remains coupled to a parallel increase in bone formation, it is sufficient to treat the osteoclast to restore bone-remodeling rates towards normal. Currently, all agents used to treat PDB are antiresorptive in nature, and include calcitonin and bisphosphonates. Even though antiresorptive therapy may reduce bone pain, symptomatic treatment with non-steroidal anti-inflammatory compounds is required in some patients to further reduce bone pain due to osteoarthritis or nerve compression. In these circumstances, patients may also

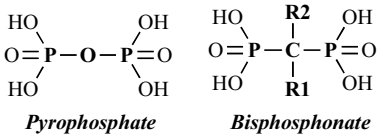

Fig. (1). Chemical structure of phyrophosphate and geminal structure of bisphosphonates. Functional R1 and R2 domains are indicated.

respond to opioid analgesics, acupuncture, electrical nerve stimulation or the use of walking aids [28]. Moreover, since new bone formation usually occurs during treatment in order to repair pagetic bone, and since hypocalcemia and hyperparathyroidism are common after the suppression of bone turnover, daily supplements of calcium and vitamin D should be also recommended to PDB patients in addition to antiresorptive therapy.

Even though calcitonin has been successfully used to treat PDB over the past years, bisphosphonates are currently considered the treatment of choice [28, 29]. Calcitonin was the first antiresorptive agent to be used for PDB (generally at daily subcutaneous 100 U injections for several months) and is still approved for the treatment of PDB. This agent has been associated with normalization of alkaline phosphatase or symptom relief in up to 50% of patients [29], but is generally less effective than the more potent bisphosphonates, has a short-term action on bone, and resistance to treatment can develop after different treatment courses. Thus, its use should possibly be reserved for the few patients with contraindications to bisphosphonates.

2.2. Bisphosphonates and Paget's Disease of Bone

Bisphosphonates are the treatment of choice of PDB, as well as of many other conditions characterized by increased bone resorption such as osteoporosis and bone metastases. These compounds are synthetic analogues of pyrophosphate that bind to hydroxyapatite in bone. In bisphosphonates, the oxygen molecule that binds the two phosphate molecules of pyrophosphate (P-O-P) is substituted by a carbon (P-C-P) (Fig. **1**). This substitution renders bisphosphonates resistant to biological degradation and therefore suitable for clinical use.

The physicochemical effects of many of the bisphosphonates are very similar to those of pyrophosphate [30, 31]. Thus, they inhibit the formation, delay the aggregation, and also slow down the dissolution of calcium phosphate crystals. All these effects are related to the marked affinity of these compounds for solid-phase calcium phosphate, on the surface of which they bind strongly. This property is of great importance, because it is the basis for the use of these compounds as skeletal markers in nuclear medicine and the basis for their selective localization in bone when used as drugs. However, bisphosphonates not only inhibit the growth and dissolution of calcium crystals but have particularly high affinity for areas of high bone turnover and inhibit osteoclast activity. Both these properties render them particularly effective in the treatment of PDB. In fact, they are much more potent antiresorptives than calcitonin, and their effects on bone turnover may persist after therapy discontinuation for months or even years.

This class of antiresorptive agents include several compounds that differs for the R1 (the bone hook) and/or R2 (the bioactive moiety) side chains that are attached to the central (geminal) carbon atom (Figs. **1** and **2**) and that are not present in pyrophosphate. Variation in phosphonate groups in R1 are responsible for selective targeting and binding of bisphosphonates to bone, while the structure of the R2 is responsible for their potency and their action on bone resorption [30]. The latter is achieved either by intracellular formation of a toxic ATP analogue, an action relevant for bisphosphonates without a nitrogen functionality in R2, or by the inhibition of farnesylpyrophosphate (FPP) synthase of the mevalonic acid metabolic pathway and subsequently the prenylation of small GTPase signaling proteins, leading to osteoclasts apoptosis (Fig. **3**), an action relevant for nitrogen-containing bisphosphonates [31-33].

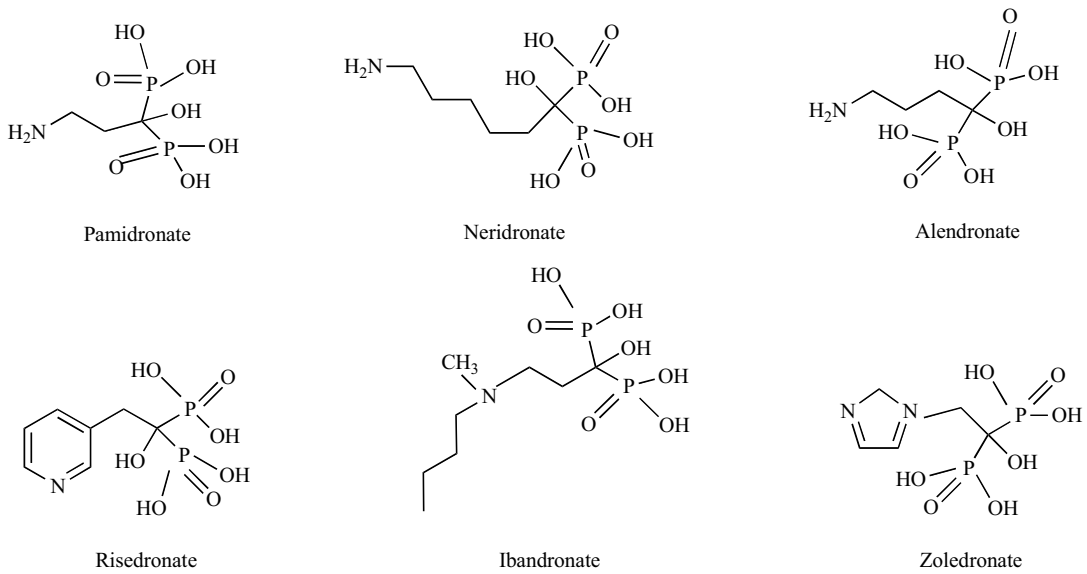

Fig. (2). Chemical structures of amino-bisphosphonates.

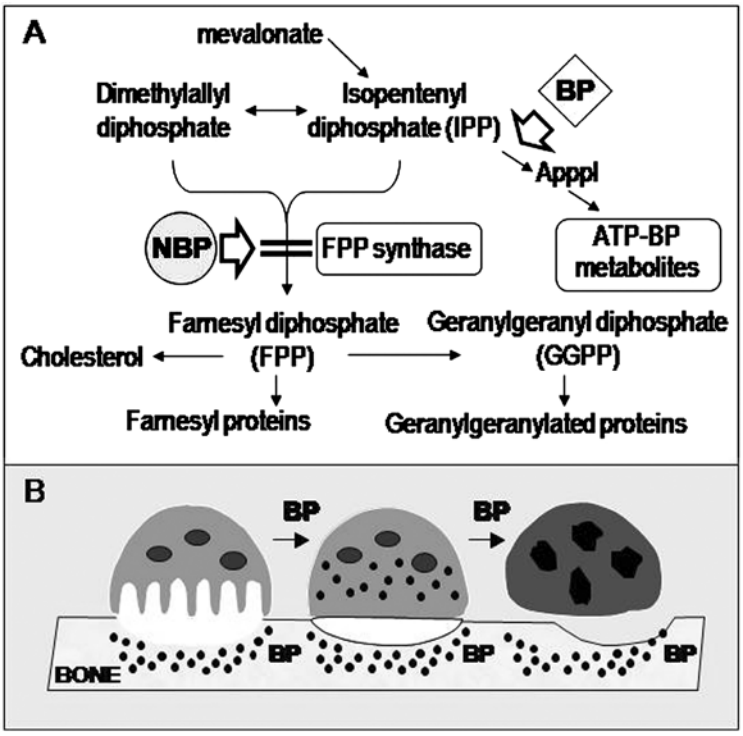

Fig. (3). Mechanism of action of bisphosphonates (BP) on osteoclasts. **A**. Mevalonate pathway and effects of amino-bishosphonates (NBPs) on FPP synthase. NBPs inhibit FPP synthase, thereby preventing the prenylation of small GTPase proteins essential for the function and survival of osteoclasts. Inhibition of FPP synthase also causes the accumulation of IPP, which is incorporated into ATP analogs. Non amino-bisphosphonates lack the inhibitory activity on FPP synthase and are metabolized in the osteoclast cytosol to ATP analogs that induce osteoclast apoptosis. **B**. After binding to bone mineral, the drugs are internalized into bone-resorbing osteoclasts by endocytosis leading to osteoclast apoptosis.

Numerous studies have demonstrated the efficacy of bisphosphonates in the management of patients with PDB. Historically, etidronate was the first bisphosphonate to be used in the treatment of PDB. At an oral daily dose of 400 mg for 6 months, with at least a 6-month drug-free interval, etidronate was associated with about 50% reduction in levels of serum alkaline phosphatase. However, because of its modest antiresorptive potency, treatment effects were transient and failure was not uncommon [34-37]. Moreover a consistent portion of patients tended to become resistant [36, 38]. Greater reductions in bone turnover were achieved with higher etidronate doses, but this is contraindicated because doses higher than 5 mg/kg/day can induce a transient focal osteomalacia [35, 36]. A slight increased efficacy was observed with tiludronate 400 mg daily for 6 months [39].

Once the potential clinical value of these first generation bisphosphonates had been appreciated, research efforts were devoted to the development of compounds with a more powerful antiresorptive activity, but without a corresponding ability to inhibit mineralization and cause osteomalacia. With compounds such as etidronate there was only a 10- to 100-fold difference between doses that inhibit mineralization compared with doses that reduce bone resorption [31]. Enhancing this window was readily achieved and more potent bisphosphonates were developed and superseded etidronate or tiludronate in the treatment of PDB. All these bisphosphonates are characterized by the presence of a basic primary nitrogen atom in the R2 side chain and are called amino-bisphosphonates. These include alendronate, risedronate, pamidronate, neridronate, and, most recently, zoledronic acid (Fig. **2**). Both alendronate (40 mg/day for 6 months) and risedronate (30 mg/day for 2 months) have been used in patients with moderate to severe PDB showing normalization of alkaline phosphatase levels in 60–70% of subjects after a course of treatment, with maintenance of biochemical remission for one year or longer in a majority of patients [40-42]. Retreatment with both these compounds may be recommended once normal levels of alkaline phosphatase rise again above normal or nadir levels (if normal levels are not achieved) rise by 25% or more [29]. The main adverse effects seen with these compounds given as oral regimens were esophageal irritation and upper gastrointestinal discomfort. Moreover, patient compliance can be impaired since both alendronate and risedronate assumption requires to fast before and after treatment because of their very low oral bioavailability and to remain upright for at least 30 minutes after dosing. These formulations could be no appropriate for patients with severe form of disease, in which a prompt suppression of disease activity is warranted. Intravenous regimens with clodronate and pamidronate partially overcame these problems, even though multiple visits and treatment courses were generally required and resistance was described in a substantial proportion of patients [29]. With the development of new intravenous bisphosphonates that have higher

potency and longer-term retention in bone, there is now the potential for treating PDB patients with intermittent dosing over longer intervals and sustained clinical remission. These approaches also presents consistent advantages with regard to patient adherence to treatment.

3. INTRAVENOUS AMINO-BISPHOSPHONATE REGIMENS FOR PAGET'S DISEASE OF BONE

3.1. Pamidronate

Pamidronate disodium has been the first amino-bisphosphonate to be used as intravenous regimen in PDB [43]. This second generation bisphosphonate requires a 2- to 3-h prolonged infusion time (30–90 mg per infusion) and has been administered in a wide range of dosing schedules, most commonly 60 to 90 mg every 3 months, 6 months or annually [29, 44]. However, the optimum dose or number of doses regimens have yet to be defined. The interval between treatment courses widely ranges from 1 month to more than 1 year [44]. Moreover, one to two doses a week on nonconsecutive days or a dose weekly for 2–3 weeks or more have been also used to deliver a total projected dose between 180 and 360 mg. Individual responses to pamidronate treatment differs based on the extent of disease and activity of the pagetic process. In many cases of moderate to severe disease, three to four 60-90-mg doses will bring indices of turnover to normal or near normal, and year-long remissions are not unusual [29]. Normalization of serum alkaline phosphatase levels is generally seen in up to 50% of patients, depending on the series and the dose regimens. In studies on patients who had not previously received bisphosphonates, the response could be higher, with biochemical normalization in up to 85% of patients with moderate disease [45-47]. Pamidronate therapy has also been reported to improve pagetic pain and overall mobility in symptomatic patients [48-50]. A study comparing a same total dose of intravenous pamidronate (180 mg for 1 year, given as 30 mg weekly for the first 6 weeks or 45 mg every 3 months) with an higher dose (360 mg for 1 year, given as 30 mg weekly for the first 6 weeks and a further 60 mg for weekly for other 3 weeks) demonstrated a dose response effect, with the more severely affected patients requiring a higher total dose for disease suppression [51]. Other studies confirmed this observation [52-54], and higher cumulative dosages of pamidronate have been used in patients with severe PDB, with contrasting results. In fact, Cundy *et al*. demonstrated that even with very high doses of pamidronate (up to 2.5 g), biochemical normalization was not achieved in 4 of 5 patients in whom other therapies were unsuccessful [55]. Similar to etidronate, reduced effectiveness with repeated treatments (tachyphylaxis or acquired resistance) has also been reported with pamidronate [30, 50, 56, 57]. In two recent studies comparing different amino-bisphosphonate treatments, a consistent part of patients with moderate to severe PDB showed lack of therapeutic response to a same dose of pamidronate (60 mg every 3 months) after 6 months of treatment [47, 58]. In keeping with previous observations [49, 52, 53, 59], biochemical relapse in these patients was dependent on initial disease severity (as assessed by total alkaline phosphatase) and on previous bisphosphonate treatment. In fact, in both studies only 14%-26% of patients with a previous bisphosphonate treatment showed therapeutic response to pamidronate after 6 months as compared to 81%-86% of subjects without previous therapy.

Importantly, even though some studies showed an adequate response to high doses of pamidronate in patients thought to be resistant to treatment [60], a narrow therapeutic range between resorption inhibition and mineralization defects has been also described for this compound [61-63]. Cumulative doses of 180-360 mg during 6 or 9 weeks have been associated with osteomalacia and increased osteoid thickness on bone biopsy in up to 40% of patients [61, 62]. Thus, repeated courses with high pamidronate doses over short time intervals should be administered with caution and cannot be considered as a treatment of choice for long term remission of severe PDB.

Even though pamidronate infusion was extensively used for many years in the treatment of PDB, the recent development of newer and more potent intravenous bisphosphonates has make possible to produce even more profound suppression of disease activity, especially in patients with severe PDB.

3.2. Neridronate

Neridronate, or neridronic acid, is an aminohexane bisphosphonate (6-amino-1-hydroxyexilidene-1,1-bisphosphonate, AHBP), officially registered in some European countries for the treatment of osteogenesis imperfecta and more recently for PDB. In *in vitro* studies this compound showed potent inhibition of bone resorption by direct effects on osteoclasts or other bone cells in the immediate microenvironment of the osteoclasts [64]. Preliminary observation also demonstrated a direct effect of this aminobisphosphonate in enhancing the differentiation of cultured osteoblasts in mature bone-forming cells [65].

Clinically, neridronate, given as intravenous, intramuscular or oral regimens, has shown remarkable efficacy in different skeletal disorders, including postmenopausal osteoporosis [66], osteogenesis imperfecta [67], as well as in the suppression of bone turnover in androgen deprivation-treated prostatic carcinoma [68] or multiple myeloma [69].

Moreover, neridronate has been also successfully used in PDB either as oral and intravenous administration. The oral dose is 400 mg daily for 1–3 months, while the intravenous dose is 15–50 mg daily for 5 days or 200 mg in a single dose or in two separate doses on consecutive days. Initial studies carried out 20 years ago demonstrated comparable efficacy of this compound in suppressing bone turnover administered either intravenously (mostly 50 mg/day over 5 days) or orally [70-73]. In subsequent short-term studies single intravenous infusions of neridronate were well tolerated and effective in decreasing bone turnover markers in a dose-related manner (from 25 to 200 mg), in patients with active PDB [74, 75]. The dosage of 200 mg gave consistently good results, even in cases in which the disease was most active, leading to normalization of alkaline phosphatase levels in more than 60% of patients [74, 75]. Moreover, in contrast to pamidronate, no correlation was found between response to treatment and basal bone turnover, and patients who had had significantly higher basal values of bone resorption markers nevertheless had biochemical responses similar to patients

with lower values [74]. A consistent reduction in bone pain at the end of these studies was also registered, and the analgesic effect was usually more pronounced in patients who had entered remission [74]. Neridronate has been also successfully used in PDB patients with acquired resistance to either etidronate or clodronate treatment [70, 71, 74]. In all the intravenous studies, neridronate infusion was safe and well tolerated, without adverse effects on mineralization nor long-term adverse reactions such as impairment of renal function or haematological abnormalities. A slight, short-lived acute phase reaction was observed in 20% of patients.

Recently, a 15 months randomized study was specifically performed to compare different intravenous bisphosphonate regimens in 90 subjects with active PDB [58]. At baseline, patients were randomly assigned to receive pamidronate (30 mg, i.v., for 2 consecutive days every 3 months; n = 60) or zoledronate (4 mg, i.v.; n = 30). After 6 months, non-responders patients to pamidronate were crossed over to zoledronate (4 mg, i.v.) or neridronate (100 mg, i.v., for 2 consecutive days). Among non-responders patients to pamidronate, a single treatment course with either neridronate or zoledronate led to the achievement of therapeutic response in more than 90% of subjects (Fig. **4**). Normalization of alkaline phosphatase levels was observed after 6 months in 80% and 83% of patients treated with neridronate or zoledronate, respectively and was maintained in most patients at 9 months. A slightly increased efficacy on the reduction of bone pain was described with both zoledronate and neridronate over pamidronate [58].

3.3. Zoledronate

Zoledronate, or zoledronic acid [1-hydroxy-2(1H-imidazol-1-yl) ethylidene bisphosphonate], is a third-generation imidazole ring containing bisphosphonate. This compound binds strongly to hydroxyapatite [76] so that it is more likely to be retained in bone during the remodeling cycle because of reattachment of bisphosphonate released during resorption. In addition, its increased potency over the other bisphosphonates in inhibiting bone resorption (through an action on the key enzyme FPP synthase) allows the use of smaller doses to maintain normal bone turnover in a focal area of PDB [77, 78].

Initial studies indicated that zoledronate is 100–850 times more potent than pamidronate and can be administered intravenously for a brief period (15–30 minutes) in an ambulatory setting [79]. Preclinical trials suggested that zoledronic acid is also safer than pamidronate in terms of renal toxicity, and confirmed its improved efficacy in suppressing bone resorption for a sustained period [80, 81]. Moreover, with the antiresorptive dose levels used in these studies there have been no detectable impairments of either bone formation or mineralization [80, 81].

The first human trial of zoledronate was performed in 16 patients with active PDB [82]. Different doses of zoledronic acid (24, 72, 216, and 400 μg) were infused in 60 ml normal saline over 60 minutes and patients were followed for 2 weeks. With the 24- and 72- μg doses there were no consistent changes in 24-hour urinary hydroxyproline/creatinine excretion (OHP) and 24-hour urinary calcium/creatinine excretion. However, a significant reduction in both resorption markers was observed with the 216 μg and 400 μg doses (20–50% in the urinary OHP and 40–70% for urinary calcium/creatinine). Not surprisingly, there were no changes in the levels of bone formation markers (total or bone specific alkaline phosphatase) over the 2-week interval that comprised the post-infusion study period. In fact, as has been reported with other bisphosphonates, the initial effect of these compounds is an inhibition of osteoclast-mediated bone resorption; while reductions in osteoblast-mediated bone

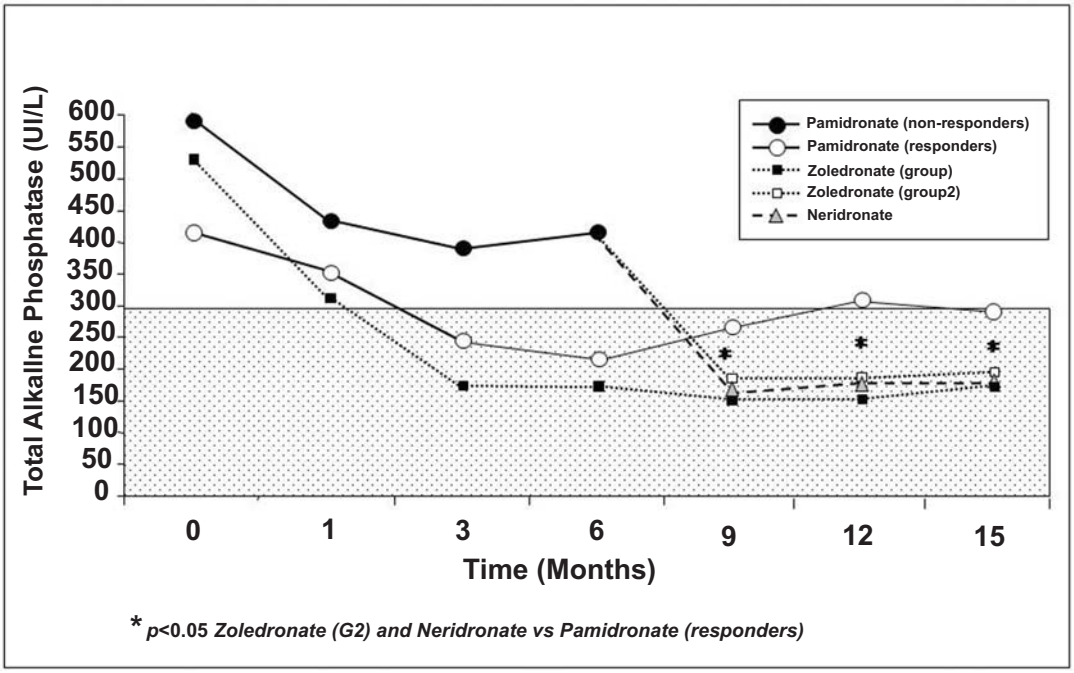

Fig. (4). Mean serum alkaline phosphatase during a 15-months study comparing intravenous neridronate and zoledronate treatment in PDB patients resistant to pamidronate. The shaded area represents the normal range of serum alkaline phosphatase (data from Merlotti *et al.* [58]).

formation generally lag behind by several weeks [34]. Following this preliminary observation a larger dose ranging study was performed over 3 months in 176 PDB patients, randomized to receive a single intravenous infusion with 50, 100, 200, or 400 μg zoledronate [83]. The primary efficacy variables were maximum percent reduction in serum alkaline phosphatase and OHP over the entire 3 months trial. A therapeutic response was defined as normalization or at least 50% reduction in baseline alkaline phosphatase levels following treatment. A rapid reduction in OHP excretion, which reached a nadir by day 10, was seen with all four treatment groups. This was followed by a fall in alkaline phosphatase which reached a nadir by day 60 with zoledronate 50, 100, and 200 μg doses, but continued to decrease at post-treatment day 90 with zoledronate 400 μg. A dose-response relationship was observed concerning the proportion of therapeutic responders. The 400 μg dose was far superior to 50 μg, 100 μg, 200 μg, and placebo and was associated with normalization of alkaline phosphatase levels in 20% and therapeutic response in 46% of patients. It was concluded, however, that the maximum effective dose for PDB was probably not achieved in this trial.

The results from a pivotal double-blinded, randomized clinical study using zoledronic acid in comparison to risedronate in patients with active PDB were released in 2005 [84]. The study design combined two identical, 6-month trials with patients either receiving a single i.v. infusion of zoledronic acid 5 mg over 15 minutes (n=177) or risedronate 30 mg daily for 2 months (n=172). The primary endpoint was the proportion of patients who achieved a therapeutic response, defined as normalization of alkaline phosphatase or a reduction of at least 75% from baseline in alkaline phosphatase excess (the difference between the measured level and the midpoint to the reference range) at 6 months. Interestingly, rates of therapeutic response were higher in zoledronate than risedronate at all time-points after 10 days, reaching 96% for zoledronate and 74% for risedronate at 6 months. The median time to a first therapeutic response was also significantly lower in the zoledronate (64 days) than risedronate (89 days) group. Normalization rates of alkaline phosphatase also showed differences between groups at all time-points from 1 month onward. At 6 months normalization was observed in 88.6% of zoledronate treated patients and 57.9% in patients in the risedronate group. Moreover, the greater response rates with zoledronate were independent of age, sex, baseline alkaline phosphatase, and previous therapy for PDB. Serum N-terminal propeptide of type I procollagen, another marker of osteoblast activity, as well as bone resorption markers (serum β-C-telopeptide and urine α-C-telopeptide of type I collagen) showed similar differences between the 2 treatment groups, confirming the increased efficacy of zoledronate over risedronate in PDB. The pattern of response was, however, different between bone resorption and bone formation markers. The nadir for the resorption markers for zoledronate was reached at the first follow-up assessment at day 10, whereas that for risedronate was reached at 2 months. In contrast, the nadirs for formation markers were reached at 3–6 months for both agents. Pain scores improved in both treatment groups, while improvement in quality of life were generally higher with zoledronate than risedronate. It might be argued, however, that the superiority of zoledronic acid observed in this study might be simply a dose-related effect. In fact, considering the differences in potency between the 2 bisphosphonates, risedronate 30 mg/day given for 60 days cannot be compared with zoledronic acid 5 mg intravenously, because the latter represents a higher effective dose. It is likely that longer courses of oral risedronate can be expected to produce high rates of normalization of bone turnover markers, as well as a longer persistence of the therapeutic effect. At the same time, a single intravenous administration of zoledronate at longer intervals (probably more than 1 year for most PDB patients) is more likely to be tolerated and to induce a better compliance compared with oral amino-bishosphonates that have to be taken daily while fasting and for several months.

A follow-up extension trial in 267 patients of the latter study confirmed the increased and sustained efficacy of single zoledronate 5 mg infusion over risedronate, given 30 mg/day for 60 days [85]. During the follow-up, zoledronate treated patients maintained the mean level of total alkaline phosphatase at the middle of the reference range, whereas those treated with risedronate showed a linear increase in total alkaline phosphatase from the 6-month post-treatment time-point. A sustained therapeutic response at 24 months from treatment was noted in 98% of patients treated with zoledronic acid compared with 57% of those treated with risedronate. Interestingly, patients treated with risedronate who had experienced prior bisphosphonate therapy seemed more vulnerable to relapse than those who were treatment naive. This trend was not seen in those treated with zoledronate, confirming the efficacy of this compound also in patients who developed a resistance to other bisphosphonate regimens. This latter point has been confirmed and extended in a 15 months study that compared the effects of intravenous infusions of pamidronate, zoledronate and neridronate in 90 subjects with active PDB [58], as previously described (Fig. **4**). The primary efficacy endpoint was the same of the previous trial comparing zoledronate to risedronate. At 6 months, 97% of patients receiving zoledronate had a therapeutic response compared with 45% of patients receiving pamidronate. Normalization of alkaline phosphatase was achieved in 93% of patients in the zoledronate group and in 35% of patients in the pamidronate group and was maintained in 79% and 65% of zoledronate-treated patients after 12 and 15 months from infusion. Moreover, zoledronate, similar to neridronate, was able to achieve therapeutic response in up to 90% of patients non-responders to pamidronate after 6 months. Interestingly, all three bisphosphonate regimens were effective in decreasing pain in a consistent group of patients (from 63% to 76%), with a slightly increased efficacy of zoledronate and neridronate over pamidronate. The response to both neridronate and zoledronate did not seem to be significantly affected by age, number of pagetic skeletal sites, or alkaline phosphatase levels. Overall, the long –term normalization rates of zoledronate observed in this study were lower than in the previous trial, possibly because of the lower zoledronate dose used (4 mg instead of 5 mg). Taken together, these results from comparative studies strongly support the use of single intravenous infusions of zoledronate as well as neridronate as a cost-effective and first-line treatment option in patients with active PDB. A slightly increased long-term efficacy of zoledronate over

neridronate was described after 18 months from treatment [86].

Of interest, in a preliminary study on 26 patients with active PDB, a single intravenous injection of zoledronate (200 or 400 mcg) not only reduced bone turnover but also directly decreased type II collagen degradation (whose expression is restricted to cartilage, not bone), suggesting a potential chondroprotective effect [87]. These data may provide an additional rationale for the use of zoledronate in PDB, given the increased prevalence of cartilage damage and osteoarthritis described in this disorder. This first report in human is in agreement with a recent experimental observation showing that subcutaneous injection of zoledronate partially protects articular cartilage from degradation in a rabbit model of inflammatory arthritis [88]. However, this hypothesis needs to be investigated in long-term studies of PDB patients monitored by radiography of the joints.

3.4. Safety

All nitrogen-containing bisphosphonates administered intravenously can induce an acute phase reaction with fever, musculoskeletal pain and other flu-like symptoms. These effects are transient and occur predominantly on first exposure to the drug in most patients who has not previously been exposed to a nitrogen-containing bisphosphonate. In fact, previous treatment with a bisphosphonate appears to provide some protection from acute phase reactions with zoledronic acid or other aminobisphosphonates [89]. This adverse event seems to be related to the accumulation of isopentenyldiphosphate (IPP, the metabolite immediately upstream of FPP synthase in the mevalonate pathway) by cells in peripheral blood (most likely monocytes), due to the inhibition of FPP synthase by nitrogen bisphosphonates. IPP is known to be a ligand for the most common subset of γδ-T cells in humans, Vγ9Vδ2 T cells [90]. Their activation perhaps *via* a selective receptor, causes the release of TNF-α and thereby initiates the proinflammatory acute-phase response. Interestingly, the activation of γδ-T cells by nitrogen bisphosphonates can be completely overcome *in vitro* by co-treating cells with statins, which prevent the accumulation of IPP [91]. Use of acetaminophen or a nonsteroidal anti-inflammatory drug is very helpful in ameliorating the self-limited flu-like symptoms.

Some reports have documented hypocalcemia occurring in patients treated with intravenous amino-bisphosphonates. This complication is generally asymptomatic and mostly occurs if patients do not take calcium and vitamin D supplements. In trials using the most potent of intravenous bisphosphonates, zoledronate, mild hypocalcemia, defined as ionized calcium concentration <1.21 mM occurred in 2–6% of patients, while only few cases experienced symptomatic hypocalcemia [58, 85]. Thus, any pre-existing hypocalcemia or condition that may impair calcium balance should be treated before therapy with zoledronic acid or other intravenous amino-bisphosphonates.

Bisphosphonates have been associated with adverse renal effects that are primarily related to dose and infusion time, with the risk increasing with higher dose and faster infusion time [92], expecially in treating patients with malignant bone disease. To date, no major long-term effects on renal function were reported with pamidronate, neridronate, and zoledronate in PDB patients with normal renal function at baseline [58]. The possibility of renal toxicity of these compounds should be borne in mind, however [93].

Osteonecrosis of the jaw (ONJ) has been identified as a potential complication, particularly with long-term, high dose intravenous bisphosphonate therapy in malignant diseases [94]. This is a rare disorder of the oral cavity that has recently been defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider [95]. To date, most cases of bisphosphonate-related ONJ (about 94%) have been reported in patients who receive monthly intravenous bisphosphonates such as pamidronate or zoledronate for the treatment of malignancies, particularly multiple myeloma and metastatic cancer [96]. Conversely, this complication seems extremely rare in patients with PDB treated with a bisphosphonate (with less than 10 cases reported to date). The etiology of ONJ is unknown and relevant prospective clinical trials to study pathogenic mechanisms are not available. Potential risk factors include long duration of exposure to bisphosphonate treatment, glucocorticoid use, recent dental extraction, invasive oral bone surgery, poorly fitting dental appliances and/or intraoral trauma, pre-existing dental or periodontal disease, cancer, anti-cancer therapy, and alcohol/tobacco abuse [95]. Based on current findings, the risk of ONJ in bisphosphonate-treated patients for osteoporosis or PDB is low (an estimated prevalence of less than one in 100,000 patient-years in non-cancer patients), and in these conditions the benefits of therapy generally far outweighs the risk. Thus healthy patients receiving bisphosphonates for PDB do not require any special dental treatment beyond routine care and standard procedures [97]. It is probably prudent for clinicians to do a routine oral examination before prescribing a bisphosphonate and to consider appropriate preventive dental care prior to treatment in patients with a history of ONJ risk factors.

There have been concerns about whether bone strength is impaired by the use of prolonged high doses of amino-bisphosphonates. In particular, some concerns about the consequences of over-suppression of bone turnover from bisphosphonates have been recently raised [98, 99] and a case report of bisphosphonate-induced osteopetrosis was published [100]. However, there are many animal studies that indicate that bisphosphonates maintain bone strength. Moreover, a recent study looking at comparable dosing of zoledronate and alendronate in a cohort of patients with osteoporosis did not evidence over-suppression of bone formation or impaired mineralization in biopsies from 23 patients [89]. To date only few transiliac bone biopsies from sites of PDB after treatment with zoledronate have been performed. There was no evidence of adynamic bone or qualitative abnormalities of bone formation in any of these biopsies, even though a slight depression of bone turnover (mineralizing surface below the reference range) was described [85, 101]. Within this context, reassuring data can be also extrapolated from a consistent number of bone biopsies and micro-CT analyses performed in a larger, phase III study (HORIZON pivotal fracture trial) involving over 7500 women with

postmenopausal osteoporosis treated with annual zoledronic acid 5mg infusion for 3 years [102, 103]. Despite a reduction in bone turnover, zoledronate treatment was associated with a better preservation of trabecular structure than placebo. Moreover, qualitative analysis revealed presence of tetracycline label in 81 of 82 biopsies from patients on zoledronic acid and all 70 biopsies from placebo patients, indicative of continued bone remodeling.

Results from the HORIZON trial also provided further indication about the safety profile of zoledronic acid [102]. Acute phase reaction occurred in 31.6% of zoledronic acid treated patients after the first infusion, 6.6% after the second infusion, and 2.8% after the third infusion. Two potential cases of ONJ were identified, one in the placebo group and one in the zoledronic acid group, with each of these resolving with antibiotic treatment and debridement. Transient and asymptomatic hypocalcemia was observed in 0.2% of treated patients. There was a transient and significant increase in serum creatinine (defined as a rise of more than 0.5 mg/dL) in 1.2% of zoledronic acid patients compared with 0.4% of placebo patients. Within 30 days after infusion, the levels returned to within 0.5 mg/dL of pre-infusion values in over 85% of patients, with the remainder of patients back to this level by the time of the next annual follow-up. Surprisingly, there were more cardiac rhythm disturbances in the group receiving zoledronic acid (266 patients, or 6.9%) than placebo (203 patients, or 5.3%; $P = 0.003$), and serious atrial fibrillation was more common with patients in the zoledronic acid group. In a subsequent phase III study [104], fewer acute phase reactions were seen, possibly due to the routine use of acetaminophen. The incidence of serum creatinine elevations > 0.5 mg/dL did not differ between the zoledronic acid and placebo groups (6.2% and 5.6%, respectively). Moreover, there was no significant difference in cardiovascular events in the two groups, and no difference in atrial fibrillation as a serious adverse event. Of interest, patients treated with zoledronic acid had a 28% lower risk of all-cause mortality than those receiving placebo (9.6% *vs*. 13.3%, $P = 0.01$).

4.4. Conclusions

Since the discovery of the profound effects of bisphosphonates on calcium metabolism, the treatment of PDB has evolved remarkably over the last several decades, from using drugs simply to reduce bone pain to using others designed to induce remission and prevent deformity and possibly other long-term complications. The overall therapeutic utility of a bisphosphonate depends upon the potency of the anti-bone resorbing properties and the dose at which the unwanted impairment of mineralization and osteomalacia occurs. This issue is particularly consistent in the treatment of PDB, where high cumulative doses are often required to achieve normal bone turnover and biochemical remission. Oral bisphosphonates are poorly absorbed from the gastrointestinal tract, usually requiring dosing in the fasting state. That fact, and the occasional gastrointestinal irritation associated with larger doses of oral bisphosphonates, further enhances the necessity of compounds that can be delivered at low concentrations and in a simplified, brief, and well-tolerated regimen. In this context, the recent development of intravenous compounds such as neridronate and zoledronate provides an improved short-term control of bone turnover as well as the maintainment of PDB remission over long-term follow-up. The potency of these agents, which provides the basis for the use of extremely small amounts, also suggests that problems with toxicity would be expected to be minimal. This approach also presents advantages with regard to outpatient management and patient adherence to treatment. Indeed, a recent survey in PDB patients evidenced inappropriate dosing regimens and short duration of treatment with oral bisphosphonates [44]. Moreover, the reduction in the incidence and severity of long-term complications such as fracture and deformity may require persistent normalization of bone turnover over many years, and this now seems a realistic possibility, particularly with zoledronate, the most potent aminobisphosphonate currently available for clinical use. In fact, the latter compound seems to maintain bone turnover within the reference range in most patients over at least 2 years from the infusion [85]. Recent preliminary observations also confirm that these regimens are also cost-effective in PDB [105].

In conclusion, the efficacy and safety demonstrated in the recent trials with neridronate and zoledronate in PDB constitutes a real progress and a cost-effective approach. Their rapid suppression of bone turnover, ease of administration, long-term effects on disease remission, as well as their good tolerance currently support the use of these aminobisphosphonates as a first-line therapeutic option in patients suffering from PDB, and particularly in those with severe polyostotic disease.

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