

Pharmacotherapy of Paget's Disease of Bone: Focus on Zoledronic Acid

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Abstract: Paget's disease of bone (PDB) affects 1%–3% of the population and is associated with increased risk for bone fracture and deformity. Increased osteoclastic activity is the principal characteristic of PDB. Bisphosphonates inhibit osteoclastic activity and represent the mainstay of treatment of PDB. Zoledronic acid, a potent member of this class, normalizes serum alkaline phosphatase (ALP) levels in the majority of patients with PDB and induces sustained disease remissions. It appears to be more effective than both risedronate and pamidronate. However, it is not clear whether bisphosphonates, including zoledronic acid, improve the clinical outcome of patients with PDB. Zoledronic acid was associated with increased risk for atrial fibrillation and osteonecrosis of the jaw in some studies in patients with osteoporosis and cancer, respectively, but not in patients with PDB. Until we have data on the effects of bisphosphonates on clinical outcomes in PDB such as fracture, deformity and osteosarcoma, we must base therapeutic decisions on the data regarding the effects of these agents on disease activity markers (such as serum ALP levels) and bone pain.

Keywords: Paget's disease of bone, bisphosphonates, zoledronic acid, risedronate, pamidronate

Introduction

Paget's disease of bone (PDB) is characterized by increased osteoclastic bone resorption that disrupts bone structure.¹ The prevalence of PDB ranges between 0.7%–3.6% in Europe^{2–5} and 1%–2% in the United States.⁶ PDB is more frequent in men and in older patients.^{2,5,7–9} In recent years, both the prevalence of PDB and its severity at presentation appear to be declining.^{2,8–11} The aetiology of PDB is largely unknown but both genetic and environmental factors appear to play a pathogenetic role.^{1,12} There is a familial clustering of PDB and up to 40% of cases have a first-degree relative with PDB.¹² Mutations in the gene encoding sequestosome 1 are present in almost half of cases of familial PDB^{13,14} and in up to 20% of patients with sporadic PDB.¹⁵ However, these mutations do not appear to be able to cause PDB without the contribution of environmental factors.¹⁶ Proposed environmental factors include viruses (particularly measles and canine distemper virus), other zoonotic agents and exposure to arsenic.^{1,12}

PDB mainly affects the pelvis, femur, lumbar spine and skull.^{1,17} PDB is associated with increased risk for deformity and fracture of pagetic bone, osteoarthritis, nerve compression and hearing loss.^{11,18,17} Congestive heart failure and osteosarcoma are more rare complications.^{11,18,17} Patients with PDB appear to have reduced life expectancy.^{11,18,17} In addition, PDB has an adverse effect on quality of life^{19,20} and is associated with high medical care costs.²¹

The primary abnormality of PDB appears to be the increased osteoclastic activity, which results in accelerated bone resorption.¹² Although this stimulates bone formation, the newly formed bone has impaired structure and reduced mechanical strength.¹² The central role of osteoclasts in the pathogenesis of PDB provides the rationale for using bisphosphonates in these patients, since bisphosphonates are potent inhibitors of osteoclastic activity.¹² Indeed, bisphosphonates currently represent the mainstay of treatment of PDB.^{1,12,22,23} Zoledronic acid is a potent bisphosphonate used in a wide range of bone diseases including postmenopausal osteoporosis,^{24–27} secondary osteoporosis due to beta thalassaemia^{28,29} and osteogenesis imperfecta.³⁰ Zoledronic acid is also approved for the treatment of hypercalcemia of malignancy, bone metastases and multiple myeloma-related bone disease.^{31–34} Zoledronic acid and other bisphosphonates appear also to be useful in other disorders, including the SAPHO syndrome (synovitis,

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acne, pustulosis, hyperostosis and osteitis),^{35,36} Gaucher disease^{37,38} and complex regional pain syndrome.^{39,40} In patients with PDB, recent studies suggest that zoledronic acid is more effective than other bisphosphonates.^{41,42} We review the role of zoledronic acid in the pharmacotherapy of PDB.

Preclinical Pharmacology of Bisphosphonates

Bisphosphonates are synthetic analogues of the naturally occurring pyrophosphate (a compound involved in the mineralization of bone), in which an oxygen atom is replaced by a carbon atom.^{43,44} This substitution prevents the enzymatic degradation of bisphosphonates.^{43,44} Bisphosphonates show a high affinity to hydroxyapatite due to the presence of a P-C-P core in their molecule.^{43,44} The addition of a hydroxyl (-OH) group at the R₁ position increases bisphosphonates' affinity to hydroxyapatite whereas the R₂ chain determines their antiresorptive potency.⁴³⁻⁴⁷ The presence of a nitrogen atom in the R₂ side chain results in a greater inhibition of osteoclastic activity.^{43,44} Six bisphosphonates are currently approved in the United States for the management of PDB, etidronate, tiludronate, pamidronate, risedronate, alendronate and zoledronic acid.²³ Etidronate and tiludronate do not contain nitrogen whereas pamidronate, risedronate, alendronate and zoledronic acid are nitrogen-containing compounds.^{22,48} Zoledronic acid has 3 nitrogen atoms in its R₂ side chain and this appears to increase its antiresorptive potency.^{43,45} Animal studies showed that zoledronic acid inhibits bone resorption more effectively than pamidronate.^{49,50} The structure of the R₂ side chain also appears to affect the binding affinity to hydroxyapatite.⁵¹ Indeed, even though zoledronic acid, alendronate, ibandronate, risedronate and etidronate have the same R₁ side chain (a hydroxyl), experimental data suggest that zoledronic acid has greater binding affinity to hydroxyapatite than the latter bisphosphonates.⁵¹ The greater binding affinity of zoledronic acid to hydroxyapatite might prolong its effects on bone turnover.^{51,52}

Non-nitrogen containing bisphosphonates have different mechanism of action than nitrogen-containing members of the class.^{44,45,48,53} The former induce apoptotic death of the osteoclasts by forming cytotoxic analogues of ATP within these cells.^{44,48} The nitrogen-containing bisphosphonates act by inhibiting farnesyl pyrophosphate synthase.^{44,53} This results in reduced post-translational prenylation of

small GTP-binding proteins, which play an important role in the survival of osteoclasts.^{44,45,48} Zoledronic acid is a more potent inhibitor of farnesyl diphosphate synthase than risedronate, ibandronate, alendronate and pamidronate and this appears to explain its greater antiresorptive ability.⁴⁵

Bisphosphonates appear to modulate the function of osteoblasts. In vitro studies showed that zoledronic acid, alendronate and ibandronate directly stimulate the differentiation and bone-forming activity of osteoblasts.⁵⁴⁻⁵⁷ In contrast, etidronate inhibited the proliferation and bone-forming activity of osteoblasts.⁵⁸ Pamidronate had stimulatory effect on osteoblasts in some studies^{56,57} but neutral or inhibitory effect in others.^{54,58} However, both zoledronic acid and pamidronate stimulated the production of osteoprotegerin from osteoblasts.⁵⁷ The effect of zoledronic acid was more pronounced.⁵⁷ Since osteoprotegerin inhibits the differentiation of osteoclasts,⁵⁹ zoledronic acid and pamidronate might act on osteoclasts indirectly, i.e. through their actions on osteoblasts.⁵⁷

Clinical Efficacy of Zoledronic Acid in Patients with PDB

In an early dose-ranging study, 16 patients with PDB received a single infusion of 24, 72, 216 or 400 µg of zoledronic acid.⁶⁰ Markers of bone resorption (24 h urinary hydroxyproline and calcium excretion) were assessed on days 1, 3, 7 and 14 post-infusion.⁶⁰ Zoledronic acid reduced both markers in a dose-dependent manner; there was no effect with the 2 lower doses (24 and 72 µg) but there was a 16%–40% and 33%–71% reduction with the 216 and 400 µg doses, respectively.⁶⁰ There was no decrease in serum alkaline phosphatase (ALP) or bone-specific ALP levels (i.e. in bone formation) during this short follow-up period.⁶⁰ In a larger placebo-controlled, dose-ranging study in 176 patients with PDB, a single infusion of 50, 100, 200 or 400 µg of zoledronic acid was administered and patients were followed-up for 90 days.⁶¹ There was a dose-dependent reduction in markers of bone resorption (urinary hydroxyproline, pyridinoline, deoxypyridinoline and calcium excretion) and bone formation (ALP and bone-specific ALP).⁶¹ The nadir in markers of bone resorption occurred at 10 days post-infusion and was followed by a reduction in markers of bone formation, which reached a nadir at 60 days.⁶¹ Response was more pronounced in patients with more active disease.⁶¹

Early case reports suggested that a single 4 mg infusion of zoledronic acid improves symptoms and normalizes ALP levels in patients with active PDB.^{62,63} In a more recent study, a single 5 mg infusion of zoledronic acid in 9 patients with PDB alleviated pain, normalized ALP levels and reduced disease activity as assessed by scintigraphy.⁶⁴ These effects were evident at 3 months and were sustained during the 12-month follow-up period.⁶⁴

Three studies compared zoledronic acid with risedronate and pamidronate in patients with PDB.^{41,42} Two identical studies compared a single 5 mg infusion of zoledronic acid with 60 days of treatment with risedronate 30 mg/day in 357 patients with PDB.⁴² Normalization of ALP levels was achieved in 96.0% and 74.3% of patients in the zoledronic acid and risedronate group, respectively ($p < 0.001$).⁴² Therapeutic response (normalization of ALP levels or $\geq 75\%$ reduction in ALP excess above the midpoint of the reference range) was achieved faster in the zoledronic acid group (in a median time of 64 days compared with 89 days in the risedronate group).⁴² Other markers of osteoblastic activity [serum levels of the N-terminal propeptide of collagen type I (PINP)] and markers of bone resorption (serum levels of the β C-telopeptide of type I collagen and the ratio of urinary α C-telopeptide of type I collagen to creatinine) also declined more in the zoledronic acid group ($p < 0.001$ for all comparisons with the risedronate group).⁴² Quality of life improved more in patients receiving zoledronic acid.⁴²

In a smaller study in 90 patients with active PDB, zoledronic acid (a single 4 mg infusion) was compared with pamidronate (30 mg IV for 2 consecutive days every 3 months).⁴¹ Serum levels of ALP, bone-specific ALP and C-terminal telopeptide of type I collagen decreased more rapidly and to a greater degree in the zoledronic acid group.⁴¹ More patients treated with zoledronic acid achieved normalization of ALP (93% vs 35% of the patients receiving pamidronate; $p < 0.001$).⁴¹ The time to nadir of ALP levels did not differ between the 2 groups.⁴¹ Response rates in the zoledronic acid group were independent of PDB severity; in contrast, in the pamidronate group, patients with higher baseline ALP levels showed lower response rates.⁴¹ In addition, the efficacy of zoledronic acid was independent of previous treatment with bisphosphonates, whereas patients in the pamidronate group who had been previously treated with other bisphosphonates

(mainly pamidronate) responded less well to pamidronate.⁴¹ Zoledronic acid normalized ALP levels in 83% of the patients who did not respond to pamidronate treatment.⁴¹ More patients reported decrease or disappearance of pain in the zoledronic acid group (97.9% vs 74.7% in the pamidronate group; $p < 0.005$).⁴¹ Quality of life did not change significantly in either group.⁴¹

There are no studies comparing zoledronic acid with the other approved bisphosphonates in patients with PDB (i.e. etidronate, tiludronate and alendronate). Risedronate was more effective than etidronate in PDB in earlier studies⁶⁵ and equally effective with tiludronate.⁶⁶ Pamidronate was equally effective with alendronate in previously untreated patients but less effective in patients who had received pamidronate in the past.⁶⁷ In zoledronic acid studies, normalization of ALP levels was achieved in 93%–96% of the patients.^{41,42} In patients treated with etidronate, alendronate, risedronate, tiludronate or pamidronate, normalization of ALP levels was observed in 15%–17%, 48%–86%, 54%–73%, 35%–74% and 56%–84% of the patients, respectively.^{65–76} It appears therefore that zoledronic acid might be more effective than other bisphosphonates in PDB. However, differences in patients' characteristics between studies preclude definite conclusions and only direct comparative studies can establish the superiority of one bisphosphonate over another.

The efficacy of zoledronic acid appears to be independent of PDB activity.^{42,41,64} In contrast, studies with etidronate, tiludronate and pamidronate showed that patients with more active disease had lower response rates and shorter remission duration.^{41,68–70,76–79}

Patients with PDB treated with etidronate and pamidronate can develop secondary resistance to these agents.^{41,65,67,77,80,81} Patients developing resistance to etidronate and pamidronate can still respond to other member of the class, including alendronate and risedronate.^{41,62,65,67,80,82} Zoledronic acid also induced biochemical remissions in patients with secondary resistance to pamidronate.^{41,62}

Regardless of the bisphosphonate used, a greater suppression of PDB activity after treatment appears to predict a longer duration of remission.^{13,70,83,84} Therefore, zoledronic acid might need to be administered less frequently than other bisphosphonates.²³ In the study that compared zoledronic acid with risedronate,⁴² patients ($n = 267$) who achieved a therapeutic response were followed-up for an

18-month extension period without receiving any additional bisphosphonate treatment.¹³ At 24 months after treatment, 98% of patients in the zoledronic acid group maintained therapeutic response compared with 57% in the risedronate group ($p < 0.0001$).¹³ Duration of remission with zoledronic acid was independent of the baseline activity of PDB and of previous treatment with other bisphosphonates.¹³ We reported that a single 4 mg infusion of zoledronic acid induced a sustained normalization of ALP levels for 3 years in a patient with active PDB.⁸⁵ In contrast, approximately 14% and 27% of patients treated with tiludronate and pamidronate, respectively, showed a relapse of ALP levels at 2 years.^{69,78} In another study, 23% of patients treated with pamidronate showed a relapse of ALP levels at 1 year.⁷⁰ Again, these studies enrolled different populations and are not directly comparable. Indeed, rates of sustained normalization of ALP levels at 15 months were similar in patients treated with zoledronic acid and in those treated with pamidronate (65% and 58%, respectively) in a study that directly compared these agents.⁴¹

Earlier studies showed that the abnormal woven structure of pagetic bones is replaced by a normal lamellar structure during long-term bisphosphonate treatment.^{86–88} Even though histological data on the effects of zoledronic acid on bone structure in patients with PDB are sparse,⁴² zoledronic acid normalized the urinary ratio of non-isomerized to β -isomerized type I collagen C-telopeptide breakdown products (CTX), suggesting an improvement in bone structure.⁸⁹ It should be mentioned that bone mineralization defects were reported in patients with PDB treated with etidronate and pamidronate.^{74,90} Etidronate might also increase the risk for pathological fracture due to the development of osteomalacia.^{91,92} In contrast, in the large study comparing zoledronic acid with risedronate, there was no evidence of adynamic bone or qualitative abnormalities in bone formation in either group.⁴²

Preliminary data suggest that zoledronic acid reduces the degradation of type II collagen, which might imply a direct chondroprotective action.⁹³ However, this action appeared to be transient.⁹³ In vitro data suggest that zoledronic acid inhibits the production of the type II collagen-degrading enzyme matrix metalloproteinase 1.⁹⁴

Osteosarcoma is a rare complication of PDB and is associated with high mortality.^{1,11,18}

Interestingly, in vitro studies showed that zoledronic acid inhibits the proliferation, induces the apoptosis and inhibits the migration and invasion of osteosarcoma cells.^{95–98} In animal studies, zoledronic acid reduced osteosarcoma growth, prevented lung metastases and prolonged survival.^{95,99,100} It is not known whether zoledronic acid reduces the risk of osteosarcoma in patients with PDB.

Despite the reduction in PDB activity with bisphosphonate treatment, it is not yet established whether these agents prevent fractures or other complications of PDB. The Paget's disease Randomized trial of Intensive versus Symptomatic Management (PRISM) was designed to address this question.¹⁰¹ In PRISM, 1,234 patients with PDB were randomized to receive symptomatic management or repeat courses of nitrogen-containing bisphosphonates (not including zoledronic acid) with the aim of normalizing serum ALP levels.¹⁰¹ The results of the PRISM study have not yet been published.

Safety and Tolerability

Zoledronic acid is administered intravenously at a dose of 5 mg.^{27,48} The duration of infusion should not be less than 15 minutes.^{27,48} Pamidronate is also administered intravenously but the dosing scheme is more cumbersome since this agent should be given over 4 h for 2 or 3 consecutive days.⁴⁸ The other bisphosphonates that are currently approved for the management of PDB (etidronate, tiludronate, risedronate and alendronate) are taken per os.²³ However, the oral administration of bisphosphonates is limited by their poor gastrointestinal absorption and the frequent occurrence of upper gastrointestinal adverse events.^{17,23,48,65,102} Accordingly, patients must stay upright and not eat anything for 30–60 minutes after taking bisphosphonates.^{17,48,102} This might compromise adherence to treatment.¹⁰³ A survey in Australia showed that discontinuation of treatment due to side effects was more common with alendronate and tiludronate than with intravenous bisphosphonates.¹⁰³ The prolonged remissions with zoledronic acid means less frequent treatment courses and might further improve compliance.

A transient acute phase reaction, comprising of myalgia and fever, may occur during infusion of zoledronic acid and can be prevented by pretreatment with acetaminophen.^{24,25,42} These symptoms occur at similar rates with pamidronate treatment.⁴¹

and appear to become milder with repeated infusions.^{24,104} Hypocalcemia may also develop after treatment with zoledronic acid^{42,64,104} and other bisphosphonates, including risedronate and pamidronate.^{42,76,79,105} Therefore, pre-existing hypocalcemia must be treated before zoledronic acid administration and there should be adequate intake of vitamin D and calcium during the first 2 weeks after treatment^{27,42,64} or even long-term.²³

In women with postmenopausal osteoporosis, zoledronic acid (3 annual 5 mg infusions) was associated with increased risk for atrial fibrillation (AF).²⁴ However, zoledronic acid studies in patients with PDB⁴² and another large study in patients with osteoporosis did not confirm this finding.²⁵ Alendronate was also associated with increased incidence of AF in some studies in osteoporosis¹⁰⁶ but not in others.^{107,108} Etidronate and risedronate do not appear to increase the risk for AF.^{42,108,109} The underlying mechanism of AF in patients treated with bisphosphonates is unclear. Bisphosphonate-induced hypocalcemia might play a role.²⁴ On the other hand, the majority of AF episodes occurred more than 30 days after the infusion of zoledronic acid suggesting that the acute-phase reaction during zoledronic acid infusion is not a major underlying mechanism.²⁴ Since osteoporosis and atherosclerosis share some similarities in their pathogenesis¹¹⁰ and atherosclerosis is an important cause of AF,¹¹¹ it was also suggested that the increased incidence of AF in patients receiving bisphosphonates might reflect the increased prevalence of atherosclerosis in this population.^{112,113}

Zoledronic acid might have adverse effects on renal function¹¹⁴ and is contraindicated in patients with creatinine clearance <35 ml/min.^{27,48} Nevertheless, in patients with PDB, serum creatinine levels declined more in those treated with zoledronic acid than in those treated with risedronate.⁴² In women with postmenopausal osteoporosis, transient increases in creatinine levels after a 5 mg zoledronic acid infusion were more frequent than after the administration of placebo.²⁴ However, this difference was not observed in other reports²⁵ and long-term changes in renal function were similar in patients treated with either zoledronic acid or placebo.²⁴

In patients with cancer, case-series and retrospective studies showed that bisphosphonates are associated with increased risk for osteonecrosis of the jaw.^{115–118} The risk appears to be greater with

intravenous than with oral bisphosphonates and greater with zoledronic acid than with pamidronate.^{116,118} However, bisphosphonates are given to patients with cancer at higher doses and more frequently than in patients with PDB.^{116–118} In patients with cancer, the risk of osteonecrosis of the jaw increased with the number of infusions and with time of exposure to bisphosphonates.¹¹⁶ Osteonecrosis of the jaw was not reported in patients with PDB treated with zoledronic acid and followed-up for 24 months.⁵² The prevalence of osteonecrosis of the jaw in patients receiving bisphosphonates for osteoporosis also appears to be low.¹¹⁹ In addition, in long-term randomized studies of annual 5 mg infusions of zoledronic acid in postmenopausal osteoporosis, osteonecrosis of the jaw was not observed²⁵ or was very rare and occurred at a similar rate in the zoledronic acid and placebo groups.²⁴

In patients with osteoporosis, subtrochanteric fractures have been reported during long-term treatment with alendronate and appear to be related to oversuppression of bone turnover.^{120–123} More studies are required to identify risk factors associated with this complication and to assess whether it also develops during long-term treatment with other bisphosphonates or in patients with PDB.

Recommendations for Treatment and Follow-up of Patients with PDB

Treatment is indicated in patients with PDB-related bone pain or neurologic complications in order to relieve symptoms.^{12,22,23,124} Some experts suggest that asymptomatic patients with lytic lesions in the skull or long bones, serum ALP levels more than twice the upper limit of normal or of young age at diagnosis should also be treated.^{12,22,23}

Most experts propose alendronate, risedronate, pamidronate or zoledronic acid as the treatment of choice in PDB whereas etidronate and tiludronate should be used as second-line agents.^{12,22,23} The biochemical treatment goal should be the normalization of ALP levels.¹²⁵ ALP levels around or below the middle of the reference range might be more preferable.¹²⁵ When there is no response to treatment after 6 months, the same or a more potent bisphosphonate should be administered.¹²⁴

After the completion of treatment with bisphosphonates, symptoms and biochemical markers of disease activity should be assessed every 3–6 months.^{22,124} These intervals might need to be

adjusted according to the bisphosphonate and activity marker used as well as on the basis of the baseline disease activity.^{22,78} Treatment with bisphosphonates should be repeated if biochemical markers of disease activity increase to 25% above the nadir reached or exceed the upper limit of normal or if symptoms persist or recur.^{22,23,124} ALP is less sensitive than other markers of PDB activity, particularly serum bone-specific ALP and PINP levels.^{78,126} However, other studies did not show clear differences.¹²⁷ In addition, due to the lower cost and wide availability of ALP, it might be preferable over these newer markers.^{22,124,125} ALP levels might be within the normal range in patients with monostotic disease.^{22,78,124,125} In this case, serum bone-specific ALP and PINP levels might still be elevated and might be useful for patient assessment and follow-up.^{22,78,124,125} Bone scintigraphy appears to be more sensitive than biochemical markers^{78,127} and could also be useful in these patients.²² Preliminary data suggest that other imaging studies, including positron emission tomography, could also be useful in selected patients with PDB.¹²⁸

Besides bisphosphonates, non-steroidal anti-inflammatory drugs can also be used in PDB in order to alleviate bone and osteoarthritic pain.^{1,17,22,124} Vitamin D and calcium supplementation are also recommended due to the excessive bone formation.^{22,48} Exercise might be beneficial but the increased risk of fractures should also be considered.⁴⁸ Surgical treatment is indicated when fractures occur, in nerve compression syndromes that do not respond to medical treatment or in selected cases of osteoarthritis or bone deformities.^{1,17,48,124} Calcitonin was the first antiresorptive agent used for PDB but is less potent than bisphosphonates and is currently indicated only in patients who cannot tolerate bisphosphonates.^{17,48}

Conclusions

Bisphosphonates are the cornerstone of treatment of PDB and zoledronic acid is one of the most effective members of this class.²³ Zoledronic acid normalizes ALP levels in the majority of patients with PDB and induces sustained disease remissions.^{41,42} It appears to be more effective than risedronate and pamidronate.^{41,42} However, it is not clear whether bisphosphonates improve the outcome of patients with PDB. Until we have data on the effects of bisphosphonates on clinical

outcomes in PDB such as fracture, deformity and osteosarcoma, we must base therapeutic decisions on the data regarding the effects of these agents on disease activity markers (such as serum ALP levels) and bone pain.

Disclosure

The authors report no conflicts of interest.

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