Current perspectives on bisphosphonate treatment in Paget’s disease of bone

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Abstract: Paget’s disease of bone is a chronic metabolic bone disease with focal increase in bone turnover. The exact etiology of the disease is uncertain, although genetic and environmental factors are believed to be important. Bisphosphonate is the main class of medication being used to control disease activity via its antiresorptive effect. This review discusses the controversies concerning the use of bisphosphonates in the treatment of Paget’s disease of bone, the efficacy of different bisphosphonates in controlling disease activity, and the possible rare side effects of bisphosphonates. Symptoms are the main indication for treatment in Paget’s disease of bone. As treatment benefits in asymptomatic individuals remain controversial and nonevidence based, the decision to treat these patients should be individualized to their risk and benefit profiles.

There are several trials conducted to evaluate and compare the efficacy of different regimes of bisphosphonates for treating Paget’s disease of bone. Most trials used biochemical markers rather than clinical symptoms or outcomes as parameters for comparison. Zoledronate is an attractive option as it can achieve high rates of biochemical remission and sustain long duration of suppression by a single dose. Atypical femoral fracture and osteonecrosis of the jaw are two rare and severe side effects reported, possibly related to the use of bisphosphonates in patients with osteoporosis and malignancy-induced hypercalcemia. As the regimes of bisphosphonates used for treating Paget’s disease of bone are different from those two diseases, the risks of developing these two possible side effects are expected to be very low, although this remains unknown. Vitamin D and calcium supplement should be given to patients at risk of vitamin D insufficiency when given zoledronate, as symptomatic hypocalcemia may develop. For those intolerant of bisphosphonates, subcutaneous calcitonin can be used for a limited period due to its associated risk of malignancy.

Keyword: osteitis deformans, antiresorptive, alkaline phosphatase

Paget’s disease of bone

Paget’s disease of bone is a chronic metabolic bone disorder that is characterized by focal areas of accelerated remodeling activity, which results in rapid bone resorption and excessive yet disorganized bone formation. It is usually diagnosed radiologically by its characteristic features of coarsening of bone trabeculae with focal osteosclerosis, cortical thickening, and bone enlargement. Typical histology of the lesion reveals a mosaic of woven and lamellar bone, with the bone marrow being replaced by periosteal fibrosis and capillary ingrowth. The elevated serum total alkaline phosphatase (ALP), due to prevailing osteoblasts activity, reflects the extent and activity of the disease. Single or multiple bones can be affected by the disease, and the typical sites of involvement include pelvis, femur, lumbar spine, skull, and tibia. The bone at the lesion is typically formed in a chaotic manner and is usually mechanically insufficient and at risk of deformity and fracture.
As yet, the exact etiology of the disease has not been well elucidated, and the speculation of it being triggered by viral infection has not been fully validated by studies. Genetic studies over the past decades have revealed that Sequestosome 1 (SQSTM1), encoding the scaffold protein p62, is the most common gene associated with increased risk of Paget’s disease of bone. Mutations of this gene were found in 20%–50% of familial cases and in about 5%–10% of sporadic cases. The role that it plays in the pathogenesis of the disease, however, remains unclear. This disease typically manifests after middle age, and the extremely rare form of juvenile Paget’s disease that presents in childhood is due to osteoprotegerin deficiency and is now considered another disease entity. For unknown reason, there is great discrepancy in the prevalence and incidence of the disease among different ethnic groups. The disease is common in the UK, Australia, North American, and Western Europe but is very rare in North Europe, Asia, and Africa. Some epidemiological data also revealed a fall in prevalence and clinical severity of the disease in developed countries, which is postulated due to changes in ethnic constitution of the population or in environmental triggers.

**Controversy on the use of bisphosphonates in treating Paget’s disease of bone**

Nitrogen-containing bisphosphonates are among the first line medications being used to treat Paget’s disease of bone. They suppress disease activity by reducing osteoclast-mediated bone resorption and bone turnover, which is reflected by the reduction or normalization of the raised serum ALP level.

Symptoms are the main indication for treating Paget’s disease of bone. They include localized pain at lesion, neurological symptoms due to deformity of vertebrae compressing on the cord or nerves, Pagetic hearing loss, high output heart failure due to extensive skeletal involvement, and hypercalcemia related to immobilization. Bisphosphonates are also recommended to be used before orthopedic intervention to the involved bone to possibly reduce blood loss.

In contrast to the situation in symptomatic cases, there has long been controversy on whether bisphosphonates given with the intention to reduce risk of developing complications in relation to disease progression is indicated or beneficial in asymptomatic cases. This issue is of particular importance as the majority of patients are asymptomatic. Based on the fact that untreated pagetic lesions may expand progressively with a reported rate of about 1 cm/year, some experts advocate the use of bisphosphonates in asymptomatic patients with lesions at sites that are likely to cause complications, such as skull, spine, weight bearing long bones, adjacent to large joints, and jaw.

Recently, a large randomized trial, Paget’s disease of bone: a randomized trial of intensive versus symptomatic management (PRISM) study, was conducted to compare the effects of symptomatic treatment with intensive bisphosphonates therapy in 1,324 patients with Paget’s disease of bone, with a median follow-up period of 3 years (ranging from 2 to 5 years). The symptomatic treatment group was treated only if they had pagetic bone pain, for which they were first given analgesics or anti-inflammatory drugs, followed by bisphosphonates if not responding. On the other hand, the intensive group received repeated courses of bisphosphonates irrespective of symptoms, with the aim of reducing and maintaining serum ALP levels within the normal range. The endpoints were quality of life, bone pain, hearing thresholds, fracture, and orthopedic surgery. As expected, the mean serum ALP level was significantly lower within 4 months of commencing treatment in the intensive treatment group than in the symptomatic treatment group and remained lower throughout the study (P<0.001).

In spite of that, there were no significant differences identified in quality of life, overall bodily pain, or in pagetic bone pain between the groups. Similarly, hearing thresholds, as assessed by audiometry, did not change significantly and did not differ between the treatment groups. Furthermore, there was no significant difference both in the incidence of clinical fractures and in the number of orthopedic surgery required between the two groups. Clinical fractures occurred in 46 of 661 patients (7.0%) in the intensive treatment group as compared with 49 of 663 patients (7.4%) in the symptomatic treatment group, and orthopedic surgery was required in 50 of 661 patients (7.3%) in the former and in 55 of 663 patients (8.3%) in the latter. It was concluded by the investigators that aiming to maintain normal ALP levels with intensive bisphosphonate therapy conferred no clinical advantage over symptom-driven management in patients with established Paget’s disease of bone.

Although several limitations of the PRISM study were recognized, including the fractures counted might not have involved Pagetic bone, 75% of the subjects were not treatment naive, the relatively short follow-up period for this chronic illness, and the limited choice of bisphosphonates, the findings of such a large, randomized trial does shed some light on the appropriate treatment aim of the disease. It seems that liberal use of bisphosphonates, aiming to gain biochemical normalization of serum ALP, conveys...
marginal clinical benefits over symptomatic treatment in most cases. Hence, in asymptomatic cases, the decision to treat or not should be based on clinical judgment of the patient’s individual risk and benefit profile and consideration of patient’s preference.

Currently, there is an ongoing multicenter, double blind, randomized, controlled trial, the Zoledronate in the Prevention of Paget’s (ZiPP) study, which investigates whether treatment with zoledronic acid in individuals carrying mutations in SQSTM1 can prevent the development of Paget’s disease of bone as defined by new bone lesion. The results of such a trial is expected to draw more discussion on the approach of prophylactic treatment in subjects genetically predisposed to Paget’s disease of bone.

**Comparison of different bisphosphonates in controlling active Paget’s disease of bone**

Bisphosphonates are analogs of inorganic pyrophosphate, which is a ubiquitous metabolite in all tissues. They bind avidly to the calcium/phosphate inorganic mineral phase of bone and are not hydrolyzed by pyrophosphatases such as bone ALP and, hence, have a sustained effect on reducing bone resorption. As the older generation of bisphosphonates such as etidronate may result in osteomalacia, aminobisphosphonates and nitrogen-containing bisphosphonates were subsequently developed. In contrast to the older bisphosphonates, nitrogen-containing bisphosphonates act differently by inhibiting farnesyl diphosphate synthase, an enzyme in the mevalonate pathway that is critical in the prenylation of small G-proteins, which mediates cytoskeletal rearrangement in osteoclasts. The newer generation of bisphosphonates include alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid.

There have been several comparative trials conducted to evaluate the efficacy of different bisphosphonates for treating Paget’s disease of bone. Most trials use biochemical markers rather than symptoms or clinical outcomes as parameters for comparison. It should be noted that biochemical remission may not necessarily transfer to potential clinical benefits or outcomes, especially when the disease activity is low or the patient is asymptomatic. In addition, other concomitant diseases such as vitamin D insufficiency that may affect the ALP level should be excluded before using it as the parameter for assessing disease activity. In the majority of studies, therapeutic response is defined as normalization of serum total ALP or suppression of excess total ALP by more than 75%, as shown in Table 1.

The oldest bisphosphonate being used to treat Paget’s disease of bone is etidronate. It is now rarely used due to its side effect of inducing osteomalacia and its relative weak antiresorptive effect. Small studies have shown that alendronate and risedronate could achieve a higher remission rate than etidronate. Pamidronate is another relatively old bisphosphonate, that has been given intravenously to treat the disease for decades. Data has shown that acquired resistance could develop in subjects with repeated courses of pamidronate treatment and resulted in progressive reduction in responsiveness. Such phenomenon is usually observed in patients with extensive Paget’s disease of bone, and the underlying mechanism is not well understood. It seems that such acquired resistance is specific to pamidronate, as it has been rarely reported to occur with other nitrogen-containing bisphosphonates.

A small comparative study on treatment-naive patients has shown that oral alendronate (40 mg/day for 3 months) and intravenous pamidronate (60 mg every 3 months), given until normalization of serum total ALP, were able to achieve biochemical remission in 86% and 56% of patients, respectively, in 1 year. It seems that oral alendronate is more effective to achieve biochemical remission by this regime comparison. The crossover of drug use in this study also showed that, among those who were unable to achieve biochemical remission after 1 year of pamidronate treatment, 10/14 (71%) patients were able to attain that with alendronate treatment.

Several trials compare the efficacy of zoledronic acid and pamidronate in achieving biochemical remission. One study has shown that one dose of intravenous zoledronic acid 4 mg could render 93% of patients to achieve normal serum total ALP after 6 month, while only 35% for those receiving intravenous pamidronate 60 mg every 3 months. The crossover part of that study has shown that either a single dose of neridronate or zoledronate infusion could normalize serum total ALP in more than 80% of patients in whom pamidronate had failed to achieve that. In another trial, a single dose of 5 mg zoledronic acid normalized the serum total ALP in 89% of patients after 6 months compared to only 58% receiving the regime of oral risedronate 30 mg daily for 60 days. A follow-up study of that cohort revealed that 98% of zoledronate-treated patients who were in remission at 6 months posttreatment remained so at 2 years posttreatment, as compared to 57% for risedronate-treated individuals; at 5–6 years posttreatment, the biochemical remission rates were 87% and 38%, respectively.

Table 1 summarizes the findings of recent comparative studies on the efficacy of different bisphosphonates.
Table 1 Summary of the studies comparing the efficacy of different bisphosphonates in treatment of active Paget’s disease of bone

<table>
<thead>
<tr>
<th>References</th>
<th>Drugs</th>
<th>Duration</th>
<th>Study</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Miller et al[22] 1999</td>
<td>RIS 30 mg daily for 2 months (n=62) versus ETI 400 mg daily for 6 months (n=61)</td>
<td>12–18 months</td>
<td>Prospective, randomized, double-blind study</td>
<td>Normalized serum ALP at 12 months and 18 months</td>
<td>1) Serum ALP normalized at 12 months in 73% of RIS group and 15% in ETI group (P&lt;0.001); 2) Median time to normalization: 91 days for RIS group, &gt;360 days in ETI group (P&lt;0.001); 3) At month 18, 53% of RIS group and 14% of ETI group remained in biochemical remission; 4) Reduction in pain posttreatment was statistically significant in RIS group, but not in ETI group</td>
</tr>
<tr>
<td>Sirs et al[23] 1996</td>
<td>6 months of ALN 40 mg daily versus ETI 400 mg daily in 89 patients</td>
<td>6 months</td>
<td>Controlled study</td>
<td>Percentage change in serum ALP, changes in urinary DPD excretion, pain, functional impairment scores, and radiological osteolysis</td>
<td>1) The ALN-treated group had significantly greater reduction in both serum ALP (79% versus 44%) and urinary DPD (75% versus 51%) than the ETI-treated group (P&lt;0.001) in both cases; 2) Normalization of serum ALP occurred more in ALN group than in ETI group (63.4% versus 17.0%; P&lt;0.001)</td>
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<tr>
<td>Walsh et al[23] 2004</td>
<td>ALN 40 mg daily in 3-month blocks versus PAM 60 mg iv 3 months, continued until biochemical remission; At 1 year, nonresponders to PAM were crossed over to ALN treatment</td>
<td>2 years</td>
<td>Randomized, open-label study</td>
<td>Biochemical remission as both ALP and urine DPD/creatinine ratios are normal; or a clear plateau effect was observed</td>
<td>1) At 1 year, biochemical remission occurs in 31/36 (86%) in ALN group and 21/36 (56%) in PAM group (P=0.017); 2) In previously untreated patients, remission was achieved in 20/22 (91%) in ALN group and 19/22 (86%) in PAM group (P&gt;0.05); 3) In previously treated patients, remission was achieved in 11/14 (79%) ALN-treated subjects and 2/14 (14%) for PAM (P&lt;0.001); 4) Of subjects crossed over to ALN, 10/14 (71%) achieved remission, including 9/11 (82%) previously treated patients</td>
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<tr>
<td>Merlotti et al[28] 2007</td>
<td>ZOL 4 mg iv (n=30) versus PAM 30 mg iv for 2 consecutive days every 3 months (n=60); After 6 months, nonresponders to PAM were crossed over to ZOL 4 mg iv once or NER 100 mg iv for 2 days</td>
<td>15 months</td>
<td>Randomized study; follow-up crossover study</td>
<td>Therapeutic response defined as normalization of ALP or a reduction of at least 75% in total ALP excess</td>
<td>1) 96% (169 of 176) patients given ZOL versus 74.3% (127 of 171) given RIS (P&lt;0.001) reached endpoint at 6 months; 2) ALP levels normalized in 88.6% ZOL-treated patients versus 57.9% for RIS (P&lt;0.001); 3) At 6 months, normalization of ALP was achieved in 93% of ZOL group and 35% of PAM group; 3) ALP normalization was maintained in 79% and 65% of ZOL-treated patients after 12 and 15 months, respectively; loss of therapeutic response in two of 30 (6%) at 12 and 15 months; 4) At 6 months, PAM nonresponders crossed over to NER (n=15) or ZOL (n=18); therapeutic response was achieved in 14 of 15 (93%) in NER group and 17 of 18 (94%) in ZOL group. Similar normalization rates for NER- (80%) and ZOL- (83%) treated subjects. Normalization and clinical response were maintained at 9 month posttreatment in both groups</td>
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<tr>
<td>Reid et al[32] 2005</td>
<td>ZOL 5 mg iv once versus RIS 30 mg/day for 60 days</td>
<td>6 months</td>
<td>Randomized control trial</td>
<td>Therapeutic response defined as normalization of ALP or a reduction of at least 75% in total ALP excess</td>
<td>1) At 6 months, 97% in ZOL group and 45% in PAM group had a therapeutic response; 2) At 6 months, normalization of ALP was achieved in 93% of ZOL group and 35% of PAM group; 3) ALP normalization was maintained in 79% and 65% of ZOL-treated patients after 12 and 15 months, respectively; loss of therapeutic response in two of 30 (6%) at 12 and 15 months; 4) At 6 months, PAM nonresponders crossed over to NER (n=15) or ZOL (n=18); therapeutic response was achieved in 14 of 15 (93%) in NER group and 17 of 18 (94%) in ZOL group. Similar normalization rates for NER- (80%) and ZOL- (83%) treated subjects. Normalization and clinical response were maintained at 9 month posttreatment in both groups</td>
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<tr>
<td>Hosking et al[33] 2007</td>
<td>ZOL 5 mg in 15-min iv infusion versus RIS 30 mg daily for 60 days (n=296)</td>
<td>Posttreatment 6–24 months without intervention</td>
<td>Follow-up study</td>
<td>Normalization or a &gt;75% reduction in the total ALP excess above the midpoint of the reference range</td>
<td>1) At 6 months posttreatment, mean total ALP in ZOL-treated group maintained at the middle reference range, but increased in RIS group; 2) At 24 months posttreatment, serum total ALP in the RIS group increased compared with 6 months posttreatment, but remained unchanged in the ZOL-treated group</td>
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<tr>
<td>Reid et al[34] 2010</td>
<td>ZOL 5 mg iv once versus RIS 30 mg/day for 60 days</td>
<td>6.5 years</td>
<td>Cohort, follow-up study</td>
<td>Times to relapse (serum total ALP level returns to within 20% of the pretreatment value); Loss of a response (response: normalization of ALP or &gt;75% reduction in its excess)</td>
<td>1) Relapse rate is 0.7% (1/152) in ZOL group and 20% (23/115) in RIS group (P&lt;0.001); 2) Loss of response rate is 12.5% (19/152) in ZOL group and 62% (71/115) in RIS group (P&lt;0.0001); 3) Changes from baseline in quality of life, were more positive in ZOL group across the follow-up period (P=0.01)</td>
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<tr>
<td>Woigt et al[35] 2000</td>
<td>ibandronate 2 mg iv bolus or infusion (n=20)</td>
<td>12 months</td>
<td>Prospective cohort study</td>
<td>Relapse defined as total ALP ≥25% increase above nadir</td>
<td>1) At 3 months, serum total ALP was normalized in 45% (9/20) patients; 2) At 12 months, relapse occurred in all patients</td>
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Abbreviations: ALN, alendronate; ALP, alkaline phosphatase; DPD, deoxypyridinoline; ETI, etidronate; iv, intravenously; NER, neridronate; PAM, pamidronate; RiS, risedronate; ZOL, zoledronic acid.
for treating Paget’s disease of bone. Nevertheless, fair comparison of the efficacy across all bisphosphonates is invalid as these trials are not head-to-head comparisons, and the disease activities of the subjects as well as the regimes of medications varied among studies. In general, the nitrogen-containing bisphosphonates have been shown to achieve high biochemical remission rates, ranging from around 75%–95% at 6–12 months posttreatment with different regimes. One can always try another bisphosphonate for nonresponders as small crossover studies have shown positive results. Zoledronate seems to be the most attractive option among all, as a single intravenous dose has been shown to achieve normalization of serum ALP level in more than 90% of cases at 6 months posttreatment and nearly 80% at 12 months.36 The other advantages are the avoidance of drug noncompliance and gastrointestinal side effects related to oral bisphosphonates, which are common in the elderly.

**Side effects of bisphosphonates**

It is well recognized that proper selection of bisphosphonates enhances individual compliance, as oral and intravenous bisphosphonates have slightly different side effect profiles.

Upper gastrointestinal irritation and esophagitis, which occurs in 20%–30% of users are common side effects of oral bisphosphonates41 while acute phase response or flu-like illness, which occurs in around 30% of those receiving the first infusion of zoledronate, is the most common one for intravenous amino-bisphosphonates.41 Symptomatic hypocalcemia can also occur when zoledronate is given to vitamin D-insufficient patients. Vitamin D and calcium supplement prior to or during the first few weeks following treatment is recommended for high risk group.42

For the past decade, there have been two rare but severe side effects reported, possibly related to the use of bisphosphonates. They are atypical subtrochanteric femoral fractures and osteonecrosis of the jaw (ONJ), which mainly develop in patients with osteoporosis and cancers treated with bisphosphonates.

Although case reports43–45 raised the plausible relationship between the use of bisphosphonates and the occurrence of atypical subtrochanteric femoral fractures in patients with osteoporosis, several retrospective analyses of clinical trials and large databases failed to show a significant increase in the total number of subtrochanteric fractures in the drug users.46–50 While it is obvious that the balance of risk and benefit is strongly in favor of the use of bisphosphonates in the osteoporotic population for prevention of osteoporotic fractures,47,51,52 its safety profile in treating Paget’s disease of bone remains unknown due to the lack of data in this patient group and the differences in the dosages and regimes used (Table 2). So far, there are no reported cases of atypical femoral fracture in bisphosphonate users with Paget’s disease of bone.

ONJ is another rare but serious side effect that is thought to be related to bisphosphonates, especially when used at high dose and intravenously to treat hypercalcemia in patients with malignancy.53 The majority of the reported cases are associated with dental procedures such as tooth extraction, or with preexisting dental diseases. Other risk factors for ONJ include concurrent malignancy, chemotherapy, radiotherapy, corticosteroid treatment, poor oral hygiene, and local infection including osteomyelitis. ONJ has been estimated to occur in 1%–10% of patients treated with intravenous bisphosphonates in cancer regimens and about 1/10,000–1/100,000 patient-years in osteoporosis doses.54 The risk of ONJ in patients with Paget’s disease of bone treated with bisphosphonates is unknown. In a systemic review of bisphosphonates-related ONJ, only three out of 368 (0.8%) reported cases occurred in patients with Paget’s disease of bone.55 From the current data, it is expected that

### Table 2 The bisphosphonate regimes for Paget’s disease of bone, osteoporosis, and hypercalcemia in malignancy

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Regimen for Paget’s disease of bone</th>
<th>Regimen for osteoporosis</th>
<th>Regime for malignancy related hypercalcemia</th>
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<tr>
<td>Oral</td>
<td></td>
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<tr>
<td>Etidronate</td>
<td>400 mg/day ×3–6 months</td>
<td>400 mg/day ×2 weeks, followed by elemental calcium 500 mg/day ×10 weeks</td>
<td>n/a</td>
</tr>
<tr>
<td>Alendronate</td>
<td>40 mg/day ×6 months</td>
<td>10 mg/day</td>
<td>n/a</td>
</tr>
<tr>
<td>Risedronate</td>
<td>30 mg/day ×2 months</td>
<td>5 mg/day</td>
<td>n/a</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>60 mg/day ×3 days</td>
<td>n/a</td>
<td>90 mg/3–4 weeks</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>6 mg/day ×2 days</td>
<td>3 mg/3 months</td>
<td>n/a</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg one dose</td>
<td>5 mg/year</td>
<td>4 mg/3–4 weeks</td>
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</table>

**Abbreviation:** n/a, not available.
the risk of developing ONJ remains very low in patients with Paget’s disease of bone treated with bisphosphonates, as the drug dosage is much lower than in cancer regimes, and treatment is usually intermittent. In spite of that, it is advisable to remind patients to perform all invasive dental procedures before starting bisphosphonates.

Other medications
As bisphosphonates may take weeks to suppress the excessive bone turnover and reduce bone pain caused by the pagetic lesion, opioid analgesics and nonsteroidal anti-inflammatory drugs can be used to provide faster and more effective pain relief.

Denosumab, a monoclonal antibody that inhibits osteoclastic bone resorption by binding to osteoblast-produced RANKL, has been suggested by a few case reports to be effective in controlling disease activity that is refractory to bisphosphonates. More data is warranted for its use in Paget’s disease of bone.

Calcitonin in injection form has been used to treat Paget’s disease of bone long before the arrival of the potent bisphosphonates. Its long-term use, however, is limited by the side effects of nausea, flushing, tachyphylaxis, and increased risk of malignancy. Presently, it is rarely used and is reserved only for those not tolerant of the more effective bisphosphonate therapy. Its use in Paget’s disease of bone is advised to be limited to up to 3 months or 6 months in exceptional circumstances, such as for patients with impending pathological fractures. It has been reported to cause an approximately 50% reduction in serum total ALP and relieve some symptoms such as alleviating bone pain, healing of osteolytic lesions, and reducing neurological complications. It is usually given at a daily dose of 100 IU subcutaneously and subsequently reduced to a maintenance dose of 50–100 IU three times per week.

Summary
For the past two decades, the advent of nitrogen-containing bisphosphonates have allowed more effective treatment to suppress the excessive bone turnover in patients with Paget’s disease of bone. The risks of developing two possible side effects of bisphosphonates, namely ONJ and atypical femoral fracture, are unknown but expected to remain very low as the regimes and dosages used are different from those in reported cases. Nevertheless, due to the lack of supporting evidence to treatment benefits, the decision to treat asymptomatic patients should be individualized with careful balance of risks and benefits.

Disclosure
The author reports no conflicts of interest in this work.

References