

Mini-review

The treatment of Paget's disease of bone

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Summary

The primary objective of Paget's disease treatment is the relief of symptoms, but treatment is also commonly prescribed to prevent the development of late complications in asymptomatic subjects with active disease (i.e., above normal serum alkaline phosphatase [bALP]). An aggressive course of treatment is recommended before surgery at the site of a pagetic lesion, the aim being to reduce as much as possible the vascularity of the lesion.

Bisphosphonates are considered the therapy of choice and the only realistic therapeutic option. All the new bisphosphonates (tiludronate, clodronate, pamidronate, alendronate, risedronate, ibandronate and zoledronate) appear to provide equivalent benefits. The degree of suppression of disease activity and the proportion of patients in whom normalisation of bALP is achieved does not depend on the potency of the individual compounds, but rather on the dose administered and the duration of the treatment. With these drugs, complete and sustained suppression of Paget's activity is achieved in 80% of patients.

KEY WORDS: *Paget, bisphosphonate, bone turnover.*

Introduction

The treatment of Paget's disease of bone (Paget's disease) is based on the use of agents capable of suppressing the abnormal activity of pagetic osteoclasts. Paget's disease was an untreatable condition until the mid-1970s when calcitonin became available and was registered in most countries for the treatment of the disease. Calcitonin was administered by subcutaneous injections at doses (100 IU/day) that were often poorly tolerated. The treatment proved able to alleviate bone pain within a few weeks, but the observed decreases in the activity of the disease, as assessed by bone turnover markers, was often inadequate (1). In the early '80s the bisphosphonate etidronate was introduced. This had to be used at sub-optimal doses (10 mg/kg/day) because at higher doses etidronate therapy is associated with the development of osteomalacic features. Thus, in a large proportion of patients, neither calcitonin nor etidronate were able to suppress the disease activity completely.

These agents were replaced in the '90s by the newer bisphosphonates (clodronate, tiludronate, pamidronate, alendronate and risedronate), progressively more potent than etidronate, and potentially able to achieve greater disease suppression and frank remission (i.e., normalisation of pagetic indices) for prolonged periods. In addition to these bisphosphonates, others have been studied in some countries (olpadronate and neridronate) or are still awaiting final registration (ibandronate, zoledronate) (2-6).

In the USA, gallium nitrate was also registered for the treatment of Paget's disease (7) and there have been some attempts to treat the disease with anti-viral agents.

In many patients the complications of Paget's disease require additional symptomatic treatments, including analgesics, anti-inflammatory drugs, and selected orthopaedic and neurosurgical interventions, but here we focus on the treatment of the metabolic disease.

Objective and treatment threshold

The primary objective of Paget's disease treatment is the relief of symptoms, and the new bisphosphonates are the agents most likely to relieve the aches and pain, excessive warmth over affected bone, headache due to skull involvement, low-back pain secondary to pagetic vertebral changes, and effects of nerve compression associated with the condition. Even though filling in of osteolytic blade-of-grass lesions in weight-bearing bones has been reported in some treated cases, bone deformities and secondary osteoarthritic lesions usually remain unchanged, and loss of hearing is unlikely to improve.

The question of whether or not to institute medical treatment to prevent the development of late complications in patients deemed to be at risk is still debated (8-10). In the past, medical intervention in patients with evidence of active disease (elevated levels of bone turnover markers) but who were totally asymptomatic was not considered strictly necessary. This attitude is now changing, for three reasons:

1. Biopsy sample studies have reported restoration of normal patterns of new bone deposition following suppression of pagetic activity. This might imply that prolonged suppression of overactivity can allow full restoration of normal lamellar bone and eventually a partial resolution of the deformities.
2. Untreated disease, in which abnormal bone turnover persists for decades, may be associated with the appearance or worsening of irreversible bone deformities, and then symptomatic disease. This has never been proven, although incomplete suppression of elevated indices of bone turnover, on older therapies, has been associated with disease progression (11). In this regard, it should be mentioned that prolonged treatment with the new bisphosphonates is followed by a normalisation of indices in most patients.
3. The safety profile, the general acceptability, and the costs of treatment with the newer bisphosphonates, especially when administered intravenously are, in Europe at least, excellent. This very low cost/benefit ratio has encouraged a less conservative attitude to definition of the treatment threshold.

According to recent recommendations on the management of

Paget's disease (8), the presence of asymptomatic but active disease (i.e., above normal serum alkaline phosphatase – bALP –) constitutes an indication for treatment aimed at preventing later complications. Others argue that the evidence does not yet support such use, because it has not been shown in clinical trials that suppression of the disease reduces progression of the deformity (9). The need for treatment might be considered more pressing when the involved skeletal sites are potentially more likely to give rise to severe problems or complications (e.g., weight-bearing bones, areas near major joints, vertebral bodies, extensive involvement of the skull). In this setting, treatment is also more warranted in younger patients, who may have to live with the disease for years. However, even in the elderly, medical treatment is justified in the presence of bone involvement very close to joints or nerve roots that might quickly (within the space of a few years) give rise to problems.

Treatment might also be indicated in some cases with normal bALP activity but with focal symptoms. We have observed a few cases presenting small (a phalange, the clavicle, part of the parietal bone) but very active monostotic lesions, in whom a first course of treatment relieved symptoms and fully suppressed bALP (even taking it to the lower end of the normal range). Although the symptoms returned within a few months (in spite of the bALP value still being well within the normal range), it was found that they could rapidly be relieved again with further courses of treatment (Figure 1).

One of the most scarring complications of surgery at the site of a pagetic lesion is severe blood loss. Although controlled studies are not available, an intense course of treatment is recommended in this situation, the aim being to reduce as much as possible the vascularity of the lesion.

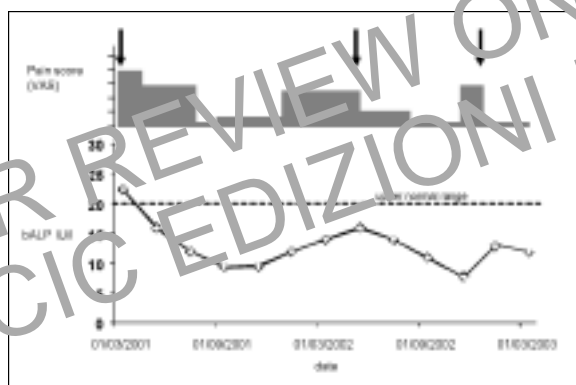


Figure 1 - Changes in pain score (Visual analogue scale, VAS) and in serum alkaline phosphatase (bALP) after single i.v. infusions of 100 mg neridronate (arrows) in a patient with focal pagetic lesion of the left parietal bone of the skull. Pain resumed despite persistent normal levels of bALP and was relieved by each neridronate infusion.

Available specific therapies

Bisphosphonates are currently regarded as the treatment of choice and the only realistic therapeutic option, but in the near future other therapies (for example, anti-RANKL agents) may become available. Here we discuss the individual compounds, considering the evidence of their efficacy and the most commonly used therapeutic regimens. With the sole exception of etidronate, the bisphosphonates appear to provide equivalent benefits. The degree of suppression of disease activity and the proportion of patients in whom the normalisation of bALP is achieved depends not on the potency of the individual com-

pounds but rather on the dose administered and the duration of the treatment. Attempts to show that patients responding poorly to one compound can respond better to another have been unconvincing (12).

Etidronate. Etidronate was the first bisphosphonate used for the clinical treatment of Paget's disease (13,14). It is still available in most countries, but is gradually being abandoned in favour of the new bisphosphonates. Etidronate is commercially available in a 200- or 400-mg tablet. The recommended regimen is 5 mg/kg/day (i.e., a daily dose of 400 mg in most patients, taken at any time of day on an empty stomach) for a period of 6 months. The main problem associated with etidronate therapy is the development of mineralisation defects. All bisphosphonates have the capacity, at high enough doses, to impair mineralisation of newly forming bone. In the case of etidronate, the doses that most effectively reduce the increased bone resorption can also impair mineralisation, thus making it necessary to administer the compound at sub-optimal doses, and for no longer than 6 months at a time. Thus, in the most severe cases, etidronate therapy is able neither to suppress disease activity adequately nor to relieve symptoms.

Tiludronate. Tiludronate is about 10 times more potent than etidronate, and its use at effective doses is not associated with mineralisation problems. In most countries it has been registered for treatment of Paget's disease as Skelid in a 200-mg tablet. The recommended dose is 400 mg daily for 3 months, followed by a 3-month post-treatment observation period, after which the bALP is likely to have reached its nadir. This approach led to a normal serum bALP at the 6-month point in a quarter of moderately affected subjects (15,16). The drug should be taken with a large glass of water in fasting conditions (at least 4 h after food) and the patient should avoid lying down for 30 minutes after ingesting it.

Pamidronate. Pamidronate has been available in the Netherlands for several decades and worldwide (in an i.v. formulation) only since the early '90s. The greater potency of pamidronate provided a number of advantages over etidronate and tiludronate, which are shared by all the newer, amino-bisphosphonates:

- it allows a majority of patients to obtain normalisation of pagetic indices rather than the partial suppression that is seen with calcitonin, etidronate, and (in most cases) tiludronate;
- the effects may be longer lasting. In some cases with monostotic disease a single treatment course is followed by an apparent permanent remission and, in most cases, up to a year or more of disease suppression;
- with pamidronate, as with all the newer, more potent bisphosphonates, the inhibition of mineralisation occurs at doses several times greater than those recommended for the treatment of Paget's disease, thus the risk of focal osteomalacia is markedly reduced;
- although the oral formulation was investigated in earlier studies carried out in Leiden by Bijvoet (17), the drug was eventually developed for the treatment of malignant hypercalcaemia, for which the i.v. formulation is considered more appropriate. Thus, the i.v. formulation remained the preferred – and indeed the only available – formulation in most European countries.

Pamidronate has a long history as a treatment for Paget's disease and in some countries, where it has been registered only for the treatment of malignant hypercalcaemia, it is still used off-label in pagetic patients. For these reasons several dosing regimens have been proposed in the literature (17-19). Where available with the indication for Paget's disease, the package insert for pamidronate, marketed as Aredia, recommends three daily 4-hour infusions, each of 30 mg in 500

ml of normal saline or 5% dextrose in water. However, in clinical practice, on the basis of accumulated experience of malignant conditions, the most common treatment is a single 60-90 mg infusion in 300-500 ml of 5% dextrose in water given over a 2-h period. In some patients with more severe disease (e.g., serum bALP levels 3-10 times normal), multiple infusions may be required. If the bALP levels are still above the normal range six months after the initial course of treatment, further infusions may be required in order to achieve complete biochemical suppression of disease activity. The most common side effect is the appearance, 24-36 hours after the first infusion, of a typical acute phase reaction (20) with low-grade fever and flu-like symptoms. The likelihood and severity of the acute phase reaction decreases progressively with repeated dosing. Transient hypocalcaemia and hypophosphataemia with secondary hyperparathyroidism may result from the intense positive skeletal calcium and phosphate balance, in relation to the uncoupling between bone resorption and bone formation. This is proportional to the Paget's disease activity and tends to occur with any bisphosphonate therapy but it is more evident when bisphosphonates are administered intravenously. Hypocalcaemia is almost invariably asymptomatic if patients are normally vitamin D repleted. In any case, it is desirable to give oral calcium supplements at a dose of 500 mg, two or three times daily, and vitamin D, 400 to 800 U daily, to prevent or counter a reduction in serum calcium and concomitant rise in PTH. There has been one report of asymptomatic mineralisation abnormalities with dosing in the usual clinical range (21), but this is not the general experience. Venous irritation may arise, especially if an insufficient volume of fluid is used or if the fluid extravasates. The rate of infusion should always be kept low in order to avoid overconcentration of the drug in the renal tubuli and renal failure, observed after i.v. infusion of clodronate and etidronate (22).

Alendronate. Alendronate is available for the treatment of Paget's disease in most western countries (Fosamax[®]). The recommended dose is 40 mg daily for 6 months to be taken with a large glass of water (>200 ml) on getting up in the morning after an overnight fast. The patient is instructed not to take anything else orally (except more water) and not to lie down for at least 30 minutes after ingesting the dose. With this dosing schedule, a single course of alendronate was found to normalise bALP in over 63% of patients with biochemical remission lasting for more than 12 months (23-25). Biopsy specimens from patients treated with alendronate revealed normal

patterns of deposition of new bone and radiological improvement (25). The overall tolerability profile is good, although upper gastrointestinal discomfort, nausea, or the less common but more serious complication of oesophageal ulceration, are not rare.

Risedronate. Risedronate 30 mg (Actonel 30) was approved by both FDA and EMEA in 1998 for the treatment of Paget's disease. Studies of risedronate have described the efficacy of a 30-mg dose given for 2 (26) or 3 (27) months to patients with moderately active disease. These short courses of therapy led to a nearly 80% reduction in bALP and normalisation of bone turnover markers in 50-70% of patients. The 30-mg risedronate dose is taken with 200 ml of water on getting up in the morning after an overnight fast, with no other oral intake (except water) and no lying down for 30 minutes after the dose. Gastrointestinal side effects of varying degrees of severity are expected in a minority of patients.

Other bisphosphonates. Other bisphosphonates have been registered or used off-label in some countries. Clodronate has been extensively investigated in the past (1, 28) and it is often used in several European countries. It is most commonly administered intravenously. The highest daily dose that can be safely infused is 300 mg dissolved in 500 ml saline solution. The rate of infusion should not exceed 200 mg/hour, in order to avoid nephrotoxic effects (22). In the moderate-severe cases, 5 to 10 infusions are usually required to achieve a 70% remission rate. Olpadronate is available only in the Netherlands and in some countries in South America (3). Neridronate is available only in Italy. Its potency is similar to that of pamidronate and the recommended dose is 100 mg in 100 ml saline solution i.v. for one or two days (4). In several European countries ibandronate and zoledronate (5, 6) are used off-label with a single i.v. bolus of 2 and 4 mg respectively.

Monitoring treatment

Treatment with bisphosphonates is associated with a rapid decrease in bone resorption markers. However, these markers are seldom used to assess treatment efficacy because they also reflect the suppression of normal bone turnover and their variance is too high (Figure 2). The markers of bone formation decline more slowly and the nadir is reached only after 6 months. It is worth noting that serum osteocalcin is only marginally increased in pagetic patients and should not be used for monitoring treatment (Figure 3).

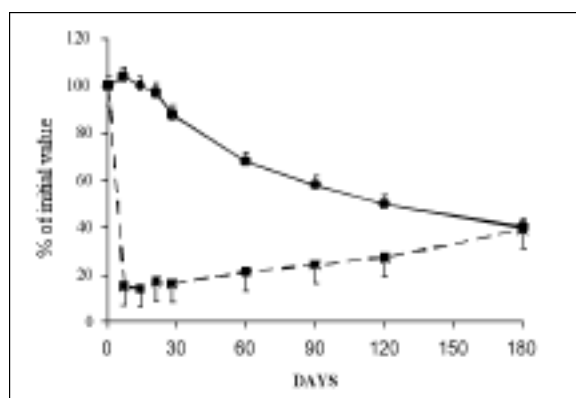


Figure 2 - Percent changes (means and standard errors) in N-telopeptide of collagen type I (dotted line) and in serum alkaline phosphatase (continuous line) after a single i.v. infusion of 100 mg neridronate at time zero in 15 patients with active Paget's disease of bone.

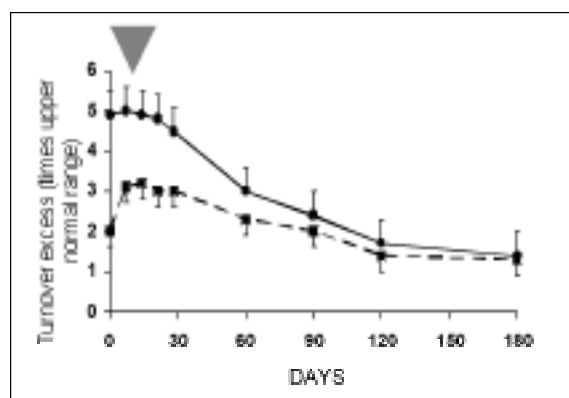


Figure 3 - Time changes (means and standard errors) in serum osteocalcin (dotted line) and in serum alkaline phosphatase (continuous line) after 5 i.v. infusions of 300 mg clodronate (arrow) in 11 patients with very active Paget's disease of bone.

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