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Medical Management of Paget's Disease of Bone: Indications for Treatment and Review of Current Therapies

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ABSTRACT: Treatment with a potent bisphosphonate is indicated in patients with Paget's disease who have symptoms likely to respond to reduced bone turnover at pagetic sites. In asymptomatic patients with active disease at sites susceptible to local progression and late complications, treatment is also recommended. Biochemical remission is achievable in a majority of patients with pamidronate, alendronate, risedronate, or zoledronic acid. Indications for medical treatment of active Paget's disease of bone include symptoms referable to sites of the disease such as bone pain, joint pain, and neurological complications; elective surgery at an active pagetic site to reduce intraoperative blood loss from highly vascular bone; management of rare instances of immobilization hypercalcemia with polyostotic disease; and presence of disease activity in asymptomatic patients at sites at risk for future complications to limit progression and possibly lower that risk. The treatment of choice is a potent nitrogen-containing bisphosphonate, including oral alendronate or risedronate or intravenous pamidronate or zoledronic acid. Etidronate and tiludronate are less potent and are second-line choices. Recent data with zoledronic acid indicate that a single infusion of 5 mg is associated with normalization of serum alkaline phosphatase in 89% of patients and a prolonged biochemical remission, making it the most effective therapy available to date. Side effect profiles with alendronate and risedronate include esophageal irritation in a minority of patients. Intravenous pamidronate and zoledronic acid may induce an acute phase reaction with fever and flu-like symptoms with the first dose, primarily in patients who are treatment naïve to nitrogen-containing bisphosphonates. Calcium and vitamin D repletion are mandatory with these potent anti-osteoclast therapies to avoid hypocalcemia. Acquired resistance to etidronate and pamidronate has been reported in some patients, leading to lesser reductions in bone turnover and shorter periods of remission, but substitution with a different bisphosphonate provides a more robust response. It is not known whether resistance to other bisphosphonates in Paget's disease occurs.
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Key words: Paget's disease, bisphosphonates, medical management, indications for treatment

INTRODUCTION

In 2001, THE AUTHORS of the present paper—three officers of the Paget Foundation for Paget's Disease of Bone and Related Disorders (ESS, KWL, FRS) and a member of the Paget Foundation's Medical Advisory Panel (PJM)—published a Perspective article in the *Journal of Bone and Mineral Research* entitled "A Clinical Approach to Diagnosis and Management of Paget's Disease of Bone."(1) That paper was the result of a request by the Professional Practice Committee of ASBMR to the Paget Foundation for a "guidelines" type document. The purpose of that paper was to provide an updated review of the epidemiology, etiology, pathology, and clinical presentation of this disease and to advise clinicians regarding both diagnosis and treatment. The sections concerning diagnostic evaluation reviewed available radiographic techniques and biochemical tests and recommended the set of tests viewed as most useful to the clinician. This was followed by a review of the evidence with respect to both efficacy and safety of medications available at that time to treat Paget's disease and an "expert opinion" position regarding the indications for treatment and a general guidance about the hierarchy of those medical treatments.

In January 2006, a symposium sponsored by the Paget Foundation entitled *Paget's Disease of Bone/Fibrous Dysplasia: Advances and Challenges* brought together experts from throughout the world to discuss our current understanding of Paget's disease, including new information on the epidemiology and etiology, pathology and clinical aspects, diagnostic tools, and treatments. Papers reflecting the content of these presentations are the basis for this supple-

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ment and offer the reader a detailed discussion of these topics that both reaffirm what was known before and describe what has been learned since 2001. This paper will focus specifically on the indications for treatment and serve as an update on the medical treatments that are available for the management of Paget's disease at this time in the United States, including a consideration of their individual levels of effectiveness and side effect profiles.

INDICATIONS FOR TREATMENT OF PAGET'S DISEASE

Paget's disease is a localized disorder of bone remodeling in which increased numbers of larger than normal-sized osteoclasts initiate an increase in bone resorption at affected skeletal sites. Rapid new bone formation follows, inducing a positive bone balance, and the bone that results is larger, architecturally disorganized, more vascular, and less structurally sound than normal bone, susceptible to deformity and fracture. Effective medical treatments work by reducing the increases in osteoclast-mediated bone resorption that characterize the disease. As a consequence, relief of many symptoms will occur, and there is the potential, albeit not yet proven, for reducing the risk of future complications. This postulated benefit would result from restoring bone remodeling and bone lamellar texture to normal or near normal and thus halting or slowing the progression of the skeletal abnormalities. The indications for treatment with antiresorptive medication that were delineated in 2001[1] continue to be recommended today. These include (1) symptoms that are caused by metabolically active Paget's disease (i.e., there is evidence of increased bone turnover and the symptom is referable to the proven site of Paget's disease). Examples are bone pain at a pagetic site including headache, limb or back pain, radicular or arthritic pain caused by bone involvement that affects nerve roots or joints, or other neurological symptoms arising in the setting of active pagetic bone impacting on neural tissue; (2) planned surgery at a metabolically active pagetic site to reduce the increased vascularity that is found in the high-turnover state, in an effort to avoid excessive bleeding during the operation; (3) hypercalcemia, an event that may rarely occur when a patient with polyostotic Paget's disease and very high bone turnover is immobilized for a period of time; (4) prevention of disease progression and reduction in future complications in patients with active Paget's disease at skeletal sites such as the skull, spine, weight-bearing long bones, and bones adjacent to major joints such as hip or knee, even in the absence of current symptoms. Complications can include bone deformity in the skull, spine, and long bones, fractures, hearing loss, pagetic arthropathy, and syndromes of neurological compression. As noted in the earlier paper, this is a controversial recommendation because it has not been proven conclusively that restoring normal turnover reduces the risk of later complications. However, it has been shown that, in the untreated state, progression of disease can occur with extension of osteolytic changes and progression of bone deformity.[2,3] Furthermore, treatment resulting in reduction of turnover to normal is associated with normal lamellar patterns of new bone deposition as seen on bone biopsy specimens,[4] and

Table 1. Therapeutic Agents for Paget's Disease of Bone

Name of agent	*Dose and administration*
Zoledronic acid (under FDA review)	Intravenous; 5 mg given over at least 15 minutes in 100 ml saline or 5% dextrose in water; retreatment guidelines not available, but if SALP remains elevated, give second dose after nadir level reached
Pamidronate (trade name: Aredia)	Intravenous; label indicates 30 mg IV over 4 h in 500 ml half-normal or normal saline or 5% dextrose in water on 3 successive days; more convenient regimen is 60–90 mg infusion (250–300 ml) over 2–4 h for 2 or more nonconsecutive days A single 90-mg infusion may suffice in mild disease; may need two to four 90-mg infusions in more severe disease. Retreat when SALP rises above normal or nadir level increases by >25%, as needed
Risedronate (trade name: Actonel)	Tablet; 30 mg once daily for 2 months Must take on empty stomach on arising in morning with 6–8 oz. plain water; may not lie down or take anything by mouth for 30 minutes after dose, then eat breakfast Retreat when SALP rises above normal or nadir level increases by >25%, as needed
Alendronate (trade name: Fosamax)	Tablet; 40 mg once daily for 6 months Must take on empty stomach on arising in morning with 6–8 oz. plain water; may not lie down or take anything by mouth for 30 minutes after dose, then eat breakfast Retreat when SALP rises above normal or nadir level increases by >25%, as needed
Tiludronate (trade name: Skelid)	Tablet; 200 mg, two tablets taken together (400 mg) once daily for 3 months Must be taken on an empty stomach with 6–8 oz of plain water, at any time of day as long as there is a 2-h period before and after dose for anything taken by mouth
Etidronate (trade name: Didronel)	Tablet; 200–400 mg once daily for 6 months Must be taken midway in a 4-hour fast with 2–3 oz of plain water; no restriction on lying down Don't give for >6 months per course; may retreat after at least 6 months off drug
Salmon calcitonin (trade name: Miacalcin)	Injection; 50–100 U subcutaneously daily or three times a week for 6–18 months Nasal spray not FDA approved for Paget's disease

there are isolated case reports of improvement in facial and skull deformities[5] and improvement in hearing loss.[6]

SPECIFIC ANTI-OSTEOCLAST THERAPY FOR PAGET'S DISEASE OF BONE

At present, two classes of compounds are available and approved for Paget's disease in the United States: bisphosphonates and calcitonin. Among the bisphosphonates are four orally administered forms: etidronate, tiludronate, alendronate, and risedronate. There are two intravenously administered bisphosphonates: pamidronate and zoledronic acid (formerly called zoledronate). A comprehensive review of the effectiveness and safety and the dosing regimens of the oral agents and pamidronate are provided in the 2001 report from the Paget Foundation described above[1]; zoledronic acid, currently under review for approval by the U.S. Food and Drug Administration (FDA), is also discussed below. Table 1 summarizes this information.

Etidronate and tiludronate are less potent agents than the other bisphosphonates, and their use at the recommended doses and durations of treatment is associated with ~50% reductions in elevated levels of serum alkaline phosphatase (SALP), the bone formation marker that is most commonly used to monitor the effects of treatment on bone turnover.[7–9] Etidronate is given generally as 400 mg/day for 6 months, with at least a 6-month drug-free interval without retreatment. With tiludronate, 400 mg/day is given for 3 months. A normal SALP occurs after a course of therapy in ~15% of patients with etidronate and was seen in 35% of those in the pivotal U.S. trial with tiludronate.[8] Greater reductions in turnover can be achieved with higher doses of etidronate, but this is contraindicated because prolonged use or doses >5 mg/kg/day can induce a transient focal osteomalacia.[10]

Both alendronate and risedronate are nitrogen-containing oral bisphosphonates and are more potent than etidronate or tiludronate. Studies in patients with moderate to severe Paget's disease have shown normalization of SALP in ~60–70% of subjects after a course of treatment,[11–13] with maintenance of biochemical remission for 18 months or longer in a majority of patients. In the U.S. trial with alendronate, 63% of patients attained biochemical remission with a normal SALP,[11] and in the risedronate pivotal trial, the value was 73%.[13] Alendronate is provided as 40 mg/day for 6 months and risedronate as 30 mg/day for 2 months. The main adverse effect seen with these compounds is esophageal irritation and upper gastrointestinal discomfort in a minority of patients. Retreatment with alendronate or risedronate is recommended once normal levels of SALP rise again above normal or nadir levels (if normal levels are not achieved) rise by >25%.

Pamidronate is an intravenous agent that requires a 2- to 3-h long infusion time, and the dose (30–90 mg per infusion) and the number of infusions are individualized to the patient.[14–16] A commonly used approach is to give 60–90 mg as a single infusion in patients with mildly elevated SALP and multiple 90-mg infusions to patients with higher degrees of abnormal turnover. The number of doses will depend on patient response. The dosing interval is primarily a function of patient and physician convenience. One to two doses a week on nonconsecutive days or a dose weekly for 2–3 weeks or more are all reasonable ways to deliver a total projected dose (180–360 mg) for moderate to severe disease, with the anticipation of a nadir level of SALP within 1–3 months after completing a course of treatment. Individual responses will vary based on the extent of disease and activity of the pagetic process. In many cases of moderate to severe disease, three to four 90-mg doses will bring indices of turnover to normal or near normal, and year-long remissions are not unusual. A normal SALP is generally seen in ~50% of patients, depending on the series. Also a nitrogen-containing bisphosphonate, pamidronate can induce an acute phase reaction with fever and flu-like symptoms after the first ever dose, but rarely with subsequent doses. Reports of osteonecrosis of the jaw, primarily in cancer patients with bone complications typically receiving very large cumulative doses of pamidronate or zoledronic acid, have recently been published[17]; this has been reported rarely in Paget's disease with pamidronate (or alendronate) given over an inappropriately long period of time with an excessive cumulative dose.[18]

The newest bisphosphonate likely to become available in the United States for Paget's disease is zoledronic acid, and it is the only member of the class not discussed in the 2001 management paper.[1] It is the most potent of the bisphosphonates for use in this disease to date. The agent is given at a dose of 5 mg, administered as a single 15-minute intravenous infusion, based on data from a clinical trial that compared the safety and efficacy of a single dose of 5 mg of zoledronic acid with 2 months of oral risedronate, 30 mg/day, in a group of 357 patients with a mean baseline SALP about four times above normal.[19] Eighty-nine percent of patients treated with zoledronic acid and 58% of those receiving risedronate had a normal SALP 6 months after initiation of therapy. The main side effects seen with zoledronic acid included a flu-like syndrome similar to that seen with pamidronate in ~10% of the subjects within the first 2–3 days after treatment. Eight patients who received zoledronic acid also had hypocalcemia, of whom two patients—neither of whom was taking prescribed calcium and vitamin D supplementation—had mild symptoms. There were no apparent renal adverse events in this trial. About 60% of those assigned to the single dose of zoledronic acid were followed without further treatment for about 1 year. All but one still maintained a therapeutic response, defined as either a normal SALP or a reduction of at least 75% from baseline in ALP excess (difference between the measured level and the midpoint of the reference range). Retreatment recommendations based on clinical trial data with zoledronic acid in Paget's disease do not exist, but it would be logical to provide additional doses of drug if the initial dose does not substantially decrease the SALP elevation after several weeks or once an escape from the initial benefit occurs. The safe total dose in a given year is not established.

Salmon calcitonin is a nonbisphosphonate treatment approved in the United States for use in Paget's disease.[20,21] It requires a subcutaneous daily injection of 100 U for sev-

eral months, a regimen typically associated with a 50% reduction in SALP and associated with symptom relief. A lowering of the dose to 50–100 U every other day is associated in most patients with maintenance of benefit. This agent is generally much less effective than the more potent bisphosphonates and requires self-injection, which has greatly limited its use in Paget's disease in recent years.

CLINICAL COMMENTS, RECOMMENDATIONS, AND CAVEATS

When treatment for Paget's disease is indicated, use of a potent bisphosphonate will provide a normal or near normal level of bone turnover in a large majority of patients, reducing many of the symptoms of the disease likely to result from the high turnover state and its effects on bone architecture and vascularity and possibly reducing the risk of late complications. The nitrogen-containing bisphosphonates, alendronate, risedronate, pamidronate, and zoledronic acid, offer the best results in management because of their greater potency—resulting in optimal nadir levels of turnover markers after a course of treatment—and the resulting potential for prolonged biochemical remissions. Once approved, zoledronic acid may be the first choice of therapy for most patients because a single infusion given over 15–20 minutes offers great convenience to the patient and has the potency to be highly effective in a substantial majority of those who receive treatment.

There are several clinical points to be emphasized with the nitrogen-containing bisphosphonates. First, calcium and vitamin D repletion must be assured to avoid hypocalcemia. Before treatment, it is reasonable to measure serum PTH and 25-hydroxyvitamin D levels to assist in determining calcium and vitamin D requirements. Second, iritis is a rare complication that has been seen with nitrogen-containing bisphosphonates. If it occurs, the agent must be discontinued, and the patient should be seen by an ophthalmologist. Further treatment with any nitrogen-containing bisphosphonate is contraindicated, but the patient can be offered one of the non–nitrogen-containing agents, either etidronate or tiludronate, which do not seem to be associated with iritis.[22] Third, all patients given pamidronate or zoledronic acid should be advised about the possibility of an acute phase reaction, typically occurring only after the initial dose and almost always in someone who has not previously been exposed to a nitrogen-containing bisphosphonate. Use of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) is very helpful in ameliorating the self-limited flu-like symptoms. Finally, physicians should be aware that acquired or secondary resistance to both etidronate and pamidronate[16,23,24] have been described, with less robust decreases in bone turnover markers or reductions in the duration of biochemical remissions or both with repeated courses of therapy. It seems that switching to a different bisphosphonate is effective in restoring a better treatment response.[24] It is unclear at this time whether acquired resistance occurs with the other approved agents.

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