Paget's Disease of Bone: An Endocrine Society Clinical Practice Guideline

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Objective: The aim of this guideline was to formulate practice guidelines for the diagnosis and treatment of Paget's disease of the bone.

Participants: The guideline was developed by an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize supporting evidence.

Conclusions: We recommend that plain radiographs be obtained of the pertinent regions of the skeleton in patients with suspected Paget's disease. If the diagnosis is confirmed, we suggest that a radionucleotide bone scan be done to determine the extent of the disease. After diagnosis of Paget's disease, we recommend measurement of serum total alkaline phosphatase or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in untreated patients. We suggest treatment with a bisphosphonate for most patients with active Paget's disease who are at risk for future complications. We suggest a single 5-mg dose of iv zoledronate as the treatment of choice in patients who have no contraindication. In patients with monostotic disease who have a normal serum total alkaline phosphatase, we suggest that a specific marker of bone formation and bone resorption be measured, although these may still be normal. Serial radionuclide bone scans may determine the response to treatment if the markers are normal. We suggest that bisphosphonate treatment may be effective in preventing or slowing the progress of hearing loss and osteoarthritis in joints adjacent to Paget's disease and may reverse paraplegia associated with spinal Paget's disease. We suggest treatment with a bisphosphonate before surgery on pagetic bone. **(*J Clin Endocrinol Metab* 99: 0000–0000, 2014)**

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Abbreviations: ALP, alkaline phosphatase; BSAP, bone-specific ALP; CTx, C-terminal propeptide of type 1 collagen; LSC, least significant change; NTx, N-terminal propeptide of type 1 collagen; P1NP, amino-terminal propeptide of type 1 collagen.

Summary of Recommendations

1.0 Diagnosis

Imaging

1.1a In patients with suspected Paget's disease, we recommend obtaining plain radiographs of the suspicious regions of the skeleton. (1|⊕⊕⊕⊕)

1.1b In patients diagnosed with Paget's disease, we suggest a radionuclide bone scan to determine the extent of the disease and identify possible asymptomatic sites. (2|⊕⊕⊕○)

Biochemistry

1.2a We recommend that after radiological diagnosis of Paget's disease, the initial biochemical evaluation of a patient should be done using serum total alkaline phosphatase (ALP) or with the use of a more specific marker of bone formation when appropriate. (1|⊕⊕⊕⊕)

1.2b We recommend measuring a specific marker of bone formation or resorption in patients with Paget's disease and abnormal liver or biliary tract function to assess response to treatment or follow evolution of the disease in untreated patients. (1|⊕⊕⊕○)

2.0 Treatment

Indications

2.1 We recommend treatment with a bisphosphonate (see Table 2) for most patients with active Paget's disease who are at risk of future complications. (1|⊕⊕⊕○)

Choice of medication

2.2 We suggest a single 5-mg dose of iv zoledronate as the treatment of choice in patients without contraindications. (2|⊕⊕⊕○)

Assessing the response to treatment

2.3 If there is urgency in the control of symptoms or the disease is particularly active, we suggest the use of short-term response of bone resorption markers before and shortly after treatment to indicate that an adequate therapeutic response is likely. (2|⊕⊕○○)

2.4 We suggest that patients who have osteolytic lesions of Paget's disease have a repeat x-ray approximately 1 year after radiological diagnosis to determine whether there has been improvement with therapy or worsening in the absence of therapy. Subsequent x-rays may be considered in the event of persistent elevations of biochemical markers of bone turnover or the presence of bone pain and to determine when there is resolution of the lesion. (2|⊕⊕○○)

Maintaining remission

2.5 We suggest that to maximize the duration of remission, bone turnover should be reduced below the midpoint of the reference range for the chosen monitoring bone turnover marker. (2|⊕⊕○○)

Relapse and retreatment

2.6 We recommend that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms. (1|⊕⊕⊕○)

Monostotic Paget's disease

2.7 We suggest that amino-terminal propeptide of type 1 collagen (P1NP) or bone-specific ALP (BSAP) and βC-terminal propeptide of type 1 collagen (βCTx) or N-terminal propeptide of type 1 collagen (NTx) should be used for assessing the activity of untreated monostotic Paget's disease, although these may be normal when evidence of disease activity is still clearly demonstrated on scintigraphy. (2|⊕⊕○○)

3.0 Management of the complications of Paget's disease

Hearing loss

3.1 We suggest treatment with a potent bisphosphonate to prevent worsening of a hearing deficit. (2|⊕⊕○○)

Osteoarthritis

3.2a We suggest the use of analgesics as adjunctive therapy for mild-to-moderate joint pain due to joint cartilage deterioration in patients with Paget's disease adjacent to the painful joint. (2|⊕⊕○○)

3.2b For patients with severe osteoarthritis adjacent to Paget's disease of bone, we suggest bisphosphonate therapy before undergoing elective total joint replacement to prevent intraoperative hemorrhaging and postoperative loosening of the prosthesis. (2|⊕⊕○○)

Bowing of lower extremity

3.3 We suggest treatment with a potent bisphosphonate before elective surgery for patients who require an osteotomy to correct severe bowing of the lower extremity associated with impaired ambulation and/or severe joint pain. (2|⊕⊕○○)

Paralysis

3.4 In cases of paraplegia associated with Paget's disease of the spine, we suggest immediate treatment with a potent iv bisphosphonate associated with neurosurgical consultation. Surgical intervention may not be necessary after effective medical treatment unless there is severe structural damage. (2|⊕⊕○○)

Neoplasms

3.5 We suggest that patients with osteosarcoma or a giant cell tumor be evaluated by an orthopedic surgeon (ungraded recommendation). If surgery is planned, we suggest pretreatment with a potent bisphosphonate to reduce bleeding from adjacent pagetic bone. (2|⊕⊕◯◯)

Congestive heart failure

3.6 We suggest treatment with a bisphosphonate in patients with Paget's disease and congestive heart failure. (2|⊕⊕◯◯)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed Paget's disease of the bone a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks,* a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

Funding for this guideline was derived solely from The Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Pathophysiology, etiology and epidemiology

Pathophysiology

Paget's disease of bone (osteitis deformans) is a chronic benign disorder of bone that generally affects one or several bones. Examination of bone specimens obtained by biopsy or autopsy indicates an evolution of the lesions, with the earliest abnormality being a focal increase in bone resorption by very large osteoclasts, followed by increased osteoblastic activity producing a high rate of bone formation resulting in bone that is less well organized than normal (3). There is some evidence for a final burned-out phase in which bone cell activity is markedly reduced and the bone structure is abnormal, with chaotic lamellar bone interspersed with woven bone. The abnormal bone structure may be associated with enlarged affected bones and skeletal deformity, particularly in weight-bearing bones.

Etiology

Studies of patients with Paget's disease indicate that there is a family history of the disorder in 5% (4) to 40%

(5), with most researchers reporting a 10–20% incidence. There is an autosomal dominant transmission pattern. Mutations in the gene-producing sequestosome 1 increase susceptibility to the development of Paget's disease (6), but there is incomplete penetrance of the disease in some family members who have been found to harbor gene mutations (7, 8). Other genes have also been implicated in increasing susceptibility to develop the disorder (9), and nearly all of the genes, including the sequestosome 1 gene, are involved in osteoclast biology.

Other investigations of the etiology of Paget's disease have focused on the potential role of chronic paramyxovirus infections contributing to the pathogenesis of the disorder (10, 11). The most impressive animal model of Paget's disease has been generated in transgenic mice by targeting measles virus nucleocapsid protein and a mutated sequestosome 1 gene into the animals (12).

Epidemiology

Paget's disease affects both men and women, with an apparent small male predominance. It rarely manifests itself clinically before age 40, and the frequency of the condition increases with advancing age. The disease is most common in Western Europe, North America, Australia, and New Zealand. Recent studies suggest a declining incidence of Paget's disease in some of these countries (13, 14). Rates vary from as low as 0.7% to as high as 4.6%. Rates in the United States are estimated to be approximately 2–3% among individuals over age 55 years (15).

Clinical features and complications

Presenting signs and symptoms

Many patients with Paget's disease of bone are asymptomatic, and the disease is discovered when a radiograph or bone scan is performed for another clinical indication or when an elevated serum ALP level is found on a multiphasic screening chemistry panel. Most of the clinical manifestations of the disorder arise from the skeleton (Table 1). Patients usually have a single bone or several bones affected by the disease (16–18). The most frequently affected bones include the pelvis, vertebrae, skull, femur, and tibia. A hallmark of the disease is skeletal deformity, which may be manifest as an increase in the size and/or abnormal shape of the bone. Bowing of the femur or tibia can occur when these bones are involved, with the disease often beginning in the proximal part of the bone and advancing distally. Increased warmth over an affected bone, usually the tibia, is attributed to increased blood flow. Skeletal growth or expansion occurs with Paget's disease of bone, becoming clinically obvious when the disease involves the skull, jaw, clavicle, femur, or tibia (19).

Table 1. Symptoms and Complications of Paget's Disease of Bone (18, 21)

System	Complication
Musculoskeletal	Bone pain
	Bone deformity
	Osteoarthritis of adjacent joints
	Acetabular protrusion
	Fractures
	Spinal stenosis
Neurological	Hearing loss
	Tinnitus
	Cranial nerve deficits (rare)
	Basilar impression
	Increased cerebrospinal fluid pressure
	Spinal stenosis
	Paraplegia, quadriplegia, vascular steal syndrome
Cardiovascular	Congestive heart failure
	Increased cardiac output
	Aortic stenosis
	Generalized atherosclerosis
	Endocardial calcification
Metabolic	Immobilization hypercalciuria
	Hypercalcemia
	Hyperuricemia
	Nephrolithiasis
Neoplasia	Sarcoma (osteosarcoma, chondrosarcoma, and fibrosarcoma)
	Giant cell tumor

Bone pain is a feature of Paget's disease of bone, usually developing late rather than early in the disease process, and it is only present in a minority of patients. The bone pain is usually mild to moderate in intensity and described as deep and aching. It can occur throughout the day and is often reported to be worse at night. Localized pain in the shaft of the femur or tibia is usually caused by the osteolytic front of the disorder and can intensify with weight bearing. In addition, skeletal pain in patients can come from osteoarthritis in joints adjacent to affected bones (20) and is either due to deformity of the articular bone or from abnormal forces transmitted to the joint from a bowed or shortened bone. Fractures with minimal trauma can occur through affected bone weakened by the elevated remodeling process with nonlamellar osteoid matrix. These fractures are termed "chalk-stick" or "banana" fractures because they are transverse and reflect the poor quality of the collagen matrix. Partial transverse or "fissure" fractures may occur along the outer curve of bowed bones. Sudden localized pain in a physically disabled femur or tibia requires an urgent x-ray to exclude an extending transverse fracture. Finally, a rare skeletal complication of Paget's disease of bone is development of osteosarcomas or other sarcomas (21). These neoplasms arise in less than 1% of patients with the disease, generally occurring in patients with multiple bones involved with Paget's disease. Benign giant cell tumors may also develop

in an affected bone but appear to be less common than sarcomas.

The most common neurological complication of Paget's disease is hearing loss associated with disease involving the skull. Originally thought to be caused by compression of the eighth cranial nerve, hearing loss is now believed to be due to cochlear damage (22, 23). With involvement of the skull, other cranial nerves can be affected. Rarely, basilar invagination may produce hydrocephalus. Paraplegia, quadriplegia, and other symptoms of spinal stenosis are rare, although the disease frequently involves vertebrae. Paralysis is often reversible and may be due to vascular steal rather than direct neurological compression.

Cardiac output can increase with widespread and active skeletal lesions, but heart failure is unusual. One study has shown that aortic stenosis, arteriosclerosis, and intracardiac calcifications are more common than in age-matched controls (24). Hypercalcemia is an unusual complication resulting when patients with more generalized skeletal disease are immobilized (16–18). More frequently, hypercalcemia due to primary hyperparathyroidism may be a concurrent problem in patients with Paget's disease (25), and other causes should also be considered. Nephrolithiasis is reported but rare. Although hyperuricemia is associated with Paget's disease, its relationship is unclear (26), as is the cause of the increased prevalence of Peyronie's disease and other fibrosing disorders (27).

The clinical features and complications of Paget's disease are closely related. Although the complications of Paget's disease are generally well recognized, presentation varies from patient to patient, so well-controlled clinical trial data specific to individual complications are generally lacking. By and large, what is available are case series with regard to specific complications and controlled trials that focus on biochemical marker data with little specificity as to individual manifestations of the condition.

1.0 Diagnosis

Imaging

1.1a In patients with suspected Paget's disease, we recommend obtaining plain radiographs of the suspicious regions of the skeleton. (1|⊕⊕⊕⊕)

1.1a Evidence

The evolution of the radiological changes in patients with Paget's disease mirror the pathological changes that evolve over time and are adequately demonstrated by x-ray evaluation (28). The earliest lesions are osteolytic and are best observed in the skull and long bones. These generally progress at about 8 mm/y (29) until the increased osteoblastic activity transforms the previous osteolytic lesion into bone with a mixed osteolytic-sclerotic appearance. In the final radiological phase of the disease, sclerosis is the dominant feature, although secondary fronts of osteolytic lesions may be noted. After decades of untreated disease, affected bones may increase in size, and lateral and anterior bowing may be seen predominantly in lower extremity long bones. Linear transverse radiolucencies termed "fissure fractures" may be seen in the convex aspect of the bowed bones. Occasionally, complete transverse fractures may develop at these sites. Experienced radiologists and physicians generally have no difficulty in distinguishing the lesions of Paget's disease from other skeletal disorders. Very seldom is it necessary to obtain a bone biopsy to make a definitive diagnosis.

Other radiological modalities, such as computerized tomography, magnetic resonance imaging, and positron emission tomography, may be useful in individual patients, particularly if a neoplasm at a pagetic site is suspected, but they are not used routinely in the evaluation of patients with Paget's disease (30).

1.1b In patients diagnosed with Paget's disease, we suggest a radionuclide bone scan to determine the extent of the disease and identify possible asymptomatic sites. (2|⊕⊕⊕◯)

1.1b Evidence

Because a majority of the lesions of Paget's disease are asymptomatic, radionuclide imaging of the skeleton rather than a general x-ray survey has become the standard means to document the extent of skeletal involvement of Paget's disease (31). It is the most sensitive test for detecting localized increased bone cell activity and may detect developing lesions before they are clearly apparent on x-rays (32). It is not recommended to repeat the test, but if treatment is administered, the radionuclide uptake of the pagetic lesions is usually reduced (33).

Biochemistry

1.2a We recommend that after radiological diagnosis of Paget's disease, the initial biochemical evaluation of a patient should be done using serum total ALP or with the use of a more specific marker of bone formation when appropriate. (1|⊕⊕⊕⊕)

1.2a Evidence

In patients who have radiological evidence of Paget's disease, the least expensive biochemical test to determine the metabolic activity of the disorder is measurement of serum total ALP. Although the increase of this bone formation marker is secondary to the change in bone resorption, it correlates well with the extent of skeletal involvement assessed from either radiographs or scintigraphy (34) and with the probability of achieving normal values with a potent bisphosphonate (35).

1.2a Values and preferences

The recommendation to use total ALP to screen for the metabolic activity of Paget's disease recognizes the low cost and universal availability of this test in both primary and secondary care. These advantages should be weighed against the greater specificity but somewhat higher cost and possibly restricted availability of more specific bone formation markers.

1.2b We recommend measuring a specific marker of bone formation or resorption in patients with Paget's disease and abnormal liver or biliary tract function to assess response to treatment or follow evolution of the disease in untreated patients. (1|⊕⊕⊕◯)

1.2b Evidence

The guideline Task Force commissioned a systematic review and meta-analysis to evaluate the utility of the available biomarkers in the care of patients with Paget's disease of the bone. In general, the biomarkers evaluated had good correlation with disease activity assessed by scintigraphy.

Serum P1NP as a measure of bone formation is the best option. If cost or availability prevent use of this option, then resorption markers such as serum βCTx or urine NTx provide accurate estimates of baseline bone metabolic activity and the response to treatment in such patients.

The disadvantage of total ALP is that there is overlap with ALP from liver. If other liver function tests are abnormal, measurement of the P1NP provides an accurate, albeit more expensive, test of bone formation. Alternative assays for assessing bone formation such as BSAP and osteocalcin are less useful than P1NP. There may be up to 20% cross-reactivity of antibodies to liver ALP with bone ALP (37, 38), and osteocalcin has been shown to be an insensitive marker for bone formation in Paget's disease (39–41).

Bone resorption markers include hydroxyproline, which has largely been abandoned for more specific measurements and replaced by a variety of telopeptides or cross-link breakdown products of type 1 collagen (40–45). These include serum α- and βCTx and urinary NTx. In untreated Paget's disease, αCTx, which contains an aspartyl-glycine motif derived from newly formed collagen, is raised proportionately more than βCTx (44), but commercial assays are not available. βCTx, which is formed from spontaneous isoaspartyl formation as the bone ages in response to treatment, is available on an automated platform and is both reproducible and relatively inexpensive, which makes it suitable for general use. However, βCTx may slightly underestimate the response to treatment of very active disease due to the isomerization phenomenon. Although urinary NTx shows large reductions during treatment, the substantial variability of individual responses, perhaps due to assay variability, may result in less discrimination than the bone formation markers (41). The advantage of telopeptide assays over bone formation assays is the much faster demonstration of a maximal decrease in bone resorption than in bone formation after treatment. Specific markers of bone turnover are also useful in patients with limited radiographic or scintigraphic evidence of Paget's disease in whom total ALP is often normal (46).

1.2b Remarks

The availability and cost of testing for bone turnover markers is an important determinant of their use, and these vary considerably by region and by insurance coverage. Practitioners may need to verify whether a given test is covered by the patient's insurance.

2.0 Treatment

Indications

2.1 We recommend treatment with a bisphosphonate (Table 2) for most patients with active Paget's disease who are at risk of future complications. (1|⊕⊕⊕◯)

2.1 Evidence

In the past, there has been a broad consensus that pharmacological treatment should be offered to patients with active disease who are either symptomatic or at significant risk of future complications (47). In addition, treatment of patients with active disease before surgery involving pagetic bone has been advised in the belief that the resultant reductions in bone vascularity decrease perioperative blood loss (47).

The increasing superiority of disease control observed with longer term follow-up of zoledronate-treated patients indicates that a re-evaluation of the indications for treatment is appropriate. Treatment regimens based on potent oral bisphosphonates or less potent iv bisphosphonates (such as pamidronate) have typically produced bio-

Table 2. Recommended Bisphosphonate Dosing Regimens

Drug	Dosage
Zoledronate[a]	5 mg given as a single infusion over 15 min. Retreatment is seldom required within 5 y
Alendronate	40 mg/d for 6 mo. Retreatment may be required between 2 and 6 y
Risedronate	30 mg/d for 2 mo. Retreatment may be required between 1 and 5 y

[a] The authors recognize that the official generic name for this drug is "zoledronic acid." However, that is a misnomer. In fact, it is the sodium salt, not the acid, that is used in medical practice. Therefore, we have elected to use "zoledronate," which is consistent with the usual nomenclature for bisphosphonates.

chemical remissions lasting 1–3 years and so have required regular follow-up of patients, typically at intervals of about 6 months. Even in patients not receiving therapy but who had active disease, regular monitoring of comparable frequency was required. Randomized trial evidence is summarized in *Section 2.2*.

2.1 Remarks

Although the specific therapy of Paget's disease is with bisphosphonates, disease complications may require surgical intervention, such as joint replacement, osteotomy for deformity, or surgical management of fractures. The indications for these interventions are similar to those in patients suffering from those problems with a nonpagetic etiology and are beyond the scope of the present guideline. Paraplegia associated with Paget's disease, however, appears to fare better when managed with bisphosphonates rather than surgery (48).

2.1 Values and preferences

Indications for medical intervention are based on cost-effectiveness and a balancing of potential benefits against potential adverse effects. In the case of iv zoledronate for Paget's disease, intervention is usually cheaper (as a result of savings in costs of follow-up investigations and clinical appointments), and results in improved quality of life. These considerations justify this course of action.

Now that it is possible to produce disease remission that can be sustained for more than 6 years in the great majority of patients, it becomes more cost-effective and more convenient to treat most patients with active disease who do not have contraindications to iv zoledronate, simply to reduce the costs and time involved in follow-up. The fact that this approach is associated with improved quality of life makes the argument even more compelling.

Choice of medication

2.2 We suggest a single 5-mg dose of iv zoledronate as the treatment of choice in patients without contraindications. (2|⊕⊕⊕◯)

2.2 Evidence

The pharmacological management of Paget's disease is primarily based on the use of drugs that reduce bone turnover, particularly bone resorption by osteoclasts. Calcitonin, a peptide hormone secreted by the C cells in the thyroid that binds directly to a receptor on the osteoclast surface, was the first effective medication to come into clinical use. Parenteral calcitonin reduces biochemical markers of bone turnover by 40–50% and leads to partial healing of lytic lesions on radiographs (49), but normalization of bone turnover is not achieved in most patients. The requirement for daily injections and the frequent occurrence of flushing or nausea limited its acceptability to patients, and disease relapse occurred rapidly after treatment cessation. As a result of these limitations, the calcitonins have been supplanted by the bisphosphonates. Nasal calcitonin is not registered for Paget's disease.

The bisphosphonate nucleus consists of two phosphate groups joined through a central carbon atom. These compounds are not subject to metabolism in humans; they bind avidly to the bone surface where they remain for several years, producing very prolonged therapeutic effects. During bone resorption, bisphosphonates are taken up by osteoclasts, where they inhibit the enzyme farnesyl pyrophosphate synthase, a critical step in the mevalonate pathway that leads to the synthesis of cholesterol as well as to the production of geranylgeraniol, which is critical to the prenylation of intracellular proteins. Disruption of this pathway adversely affects the osteoclast cytoskeleton and can result in osteoclast apoptosis. The clinical potency of a bisphosphonate is determined by its affinity for hydroxyapatite (which determines skeletal uptake) and the potency of its inhibition of farnesyl pyrophosphate synthase (50, 51). Of the bisphosphonates in clinical use, zoledronate is the most potent enzyme inhibitor and has the highest affinity for bone mineral, the latter also conferring a very long duration of action.

Etidronate was the first bisphosphonate to be used in Paget's disease. It produced greater and more durable reductions in bone turnover than calcitonin (52, 53). However, the doses necessary to produce biochemical remission in many patients also resulted in the development of osteomalacia (53–55), so other bisphosphonates were developed that had a greater antiresorptive potency relative to their inhibition of mineralization.

Clodronate and tiludronate did not cause osteomalacia but lacked sufficient potency to normalize bone turnover in all patients. Subsequent drugs incorporated a nitrogen atom into the bisphosphonate side chain, creating the amino-bisphosphonates that had much greater antiresorptive potency. Thus, pamidronate was shown to normalize bone resorption with 1 week of oral dosing, although normalization of bone formation took 3–6 months (56). Reductions in bone turnover were confirmed on bone biopsy, and healing of lytic radiological lesions was subsequently demonstrated (57). Alendronate was studied in two randomized trials, one comparing the drug with placebo (58) and the other comparing it with etidronate (59). Oral alendronate (40 mg/d for 6 mo) normalized ALP in 60–70% of patients, led to healing of lytic radiological lesions, and restored normal lamellar bone histology. Thus, the normalization of biochemical markers was associated with histological and radiological evidence of arrest of disease

progression. Risedronate tablets (30 mg/d for 2–3 mo) were evaluated in open studies (60–62) and in a randomized trial comparing risedronate with etidronate (63). ALP was normalized in 73% of patients, and there was evidence of relief of pagetic pain. However, the comparatively high doses of oral bisphosphonates required for the control of Paget's disease caused significant upper gastrointestinal side effects. As a result, there was ongoing interest in the use of iv bisphosphonates.

Ibandronate has been shown to provide effective short-term control of Paget's disease (41), but it has not been actively promoted for this indication. The major agent in this class is zoledronate, which is theoretically attractive because of its high potency and long duration of action (50, 51). A single, iv 5-mg dose of zoledronate has been compared with risedronate (30 mg/d for 2 months) in two clinical trials (64). The core study was of 6-month duration, with 96% of patients randomized to zoledronate showing a therapeutic response compared with 74% of those randomized to risedronate ($P < .001$). ALP levels normalized in 89% of patients in the zoledronate group and 58% of those given risedronate ($P < .001$). Zoledronate showed a more rapid onset of action, and superior effects on quality of life, including pain relief. Individuals with a therapeutic response in the core study entered a follow-up study that compared the duration of remissions with these two treatments. At 2 years after drug administration, therapeutic response was maintained in 98% of those receiving zoledronate and in 57% of risedronate-treated patients (65). At 5 to 6 years, these figures were 87 and 38%, respectively (66). Although the mean P1NP value remained within the normal range in the zoledronate group throughout follow-up, there were gradual increases in turnover in the risedronate cohort. Those patients who had a P1NP of <40 μg/L or a total ALP activity of <80 IU/L 6 months after treatment with zoledronate were found to have a >90% likelihood of nonrelapse during follow-up. In addition, the patients randomized to zoledronate showed consistently higher scores for the Short Form Health Survey, a measure of quality of life, than those originally randomized to risedronate (66). Thus, zoledronate produces more frequent, more complete, and more sustained responses to therapy than have been possible hitherto, allowing normalization of turnover markers and improvements in quality of life for many years in most patients after only a single infusion.

The results from the zoledronate phase 3 trials (64) suggest that a broadening of indications for treatment might be appropriate. The demonstration of more rapid, more frequent, and much more sustained disease control after a single iv infusion recommends zoledronate in preference to risedronate. The fact that risedronate is itself a very potent bisphosphonate suggests that zoledronate will maintain a comparable superiority over other available oral agents.

Zoledronate has a satisfactory safety profile, the most common adverse event being a flu-like illness, which occurs in about 25% of patients (64). Patients need to be warned of this possibility. The frequency and severity of these reactions is reduced by about one-half with acetaminophen or nonsteroidal anti-inflammatory drugs, which can be used prophylactically (67). Uveitis and other inflammatory changes in the eye can be a part of the acute phase response (68), occurring in approximately 1% of patients receiving zoledronate. This requires prompt attention from an ophthalmologist and resolves rapidly and completely with topical steroids (69). Zoledronate is potentially nephrotoxic, so it should not be administered if the glomerular filtration rate is <35 mL/min (70). Some physicians use lower doses and longer infusion times in patients with marginal renal function, but this has not been approved by regulatory agencies. Potent bisphosphonates can produce symptomatic hypocalcemia in the presence of marked vitamin D deficiency (25-hydroxyvitamin D <25 nmol/L). In those at risk of vitamin D deficiency, supplementation before treatment is advisable. A single, large, oral dose of calciferol, 100 000 U, appears to be satisfactory (47, 71).

2.2 Remarks

It is desirable that treatment efficacy should be evaluated using event-driven endpoints. Such data are less available in Paget's disease than in some other conditions, and many trials have used bone turnover markers as the primary endpoint. However, there is evidence that potent bisphosphonates produce objective improvement in bone histology, radiographic lytic lesions, bone scintigraphy, pain, and quality of life, and that these changes are reflected in changes in markers. There is no possibility of studies appropriately powered to address harder endpoints (such as frequency of joint replacement) in the foreseeable future, so decisions must be based on these available data.

2.2 Values and preferences

Some patients have contraindications to the use of iv zoledronate, such as marked renal impairment. In such individuals, oral bisphosphonates represent a much safer option because the peak serum drug concentration is substantially lower, with an accompanying reduction in the risk of renal tubular toxicity. The possibility of an acute phase response is a concern with some patients, although in general the frequency and severity are comparable to the gastrointestinal side effects associated with oral dosing; it

has the advantage of lasting only a few days in most cases. In patients in whom iv zoledronate is not an option, treatment should be targeted to those who are symptomatic or at risk of significant complications (eg, premature arthritis, fracture, or deformity). The potential benefits of intervention need to be balanced against the potential risks associated with drug therapy. Calcitonin, etidronate, and pamidronate are available therapies but are seldom used because of the ease of use and/or greater potency of zoledronate.

Assessing the response to treatment

2.3 If there is urgency in the control of symptoms or the disease is particularly active, we suggest the use of short-term response of bone resorption markers before and shortly after treatment to indicate that an adequate therapeutic response is likely. (2|⊕⊕◯◯)

2.3 Evidence

Although total ALP is the least expensive test for routine use to monitor the response to treatment, and more specific formation markers are useful when appropriate, there are occasions in which measurement of bone resorption markers is useful because they respond more rapidly than total ALP or other formation markers. Examples of the need for an early assessment of response include the presence of severe symptoms, such as spinal compression, and concerns about the ability to control very active disease. Bone resorption markers such as βCTx fall rapidly in response to potent bisphosphonates, reaching a nadir value at 10 days, whereas the response of formation markers such as total ALP is slower, reaching a nadir at about 2 to 3 months (64).

The achievement of normal bone turnover depends on disease activity and drug potency. Incomplete responses may occur with very active and extensive disease (35), but this is less of a problem with currently available potent amino bisphosphonates (64, 72). The rate of decline in bone turnover shows considerable interpatient variability, which probably reflects the sensitivity of bone cells to therapy. However, within an individual, the time it takes for the turnover to decrease by half is inversely proportional to the bisphosphonate dose per unit time and its intrinsic potency, but it is independent of the pretreatment disease activity (73, 74). The likely duration of treatment response can be predicted from the short-term (10-d) reduction in bone turnover markers such as urinary NTx, which correlates well with the final post-treatment ALP (75).

High turnover disease requires short-term treatment with a very potent bisphosphonate (ie, one dose of zoledronate). Although longer treatment with a less active drug might be effective, this is not recommended because such drugs may not decrease bone turnover into the normal range in patients with the highest rates of bone turnover.

2.3 Remarks

Although most patients will achieve normal bone turnover with currently available drugs, there are a few situations where the rate of change of turnover markers is clinically useful.

2.3 Values and preferences

Treatment induces a more rapid decrease in resorption markers compared with formation markers. For most patients, measurement of total ALP or other baseline disease activity markers at 6 to12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option. Maximal suppression of high bone turnover may require measurement at 6 months.

2.4 We suggest that patients who have osteolytic lesions of Paget's disease have a repeat x-ray approximately 1 year after radiological diagnosis to determine whether there has been improvement with therapy or worsening in the absence of therapy. Subsequent x-rays may be considered in the event of persistent elevations of biochemical markers of bone turnover or the presence of bone pain and to determine when there is resolution of the lesion. (2|⊕⊕◯◯)

2.4 Evidence

Uncontrolled trials indicate that calcitonin (76), pamidronate (57, 77), and risedronate (78) are highly effective in reversing or stabilizing osteolytic lesions of Paget's disease. A controlled trial has demonstrated the effectiveness of alendronate in reversing osteolytic lesions (58). Three months after an initial course of pamidronate, there was remission of osteolytic lesions, but after 2 years, a relapse of osteolytic lesions in many patients was noted (77). Discontinuation of calcitonin therapy is also generally followed by resumption of the osteolytic process as detected by x-rays, but additional calcitonin therapy again produces a healing response. Such beneficial responses are generally not seen with the earliest available bisphosphonate, disodium etidronate. The osteolytic lesions often worsen despite reduction of biochemical markers of bone turnover (76), perhaps related to impaired bone mineralization induced by the drug.

Maintaining remission

2.5 We suggest that to maximize the duration of remission, bone turnover should be reduced below the midpoint of the reference range for the chosen monitoring bone turnover marker. (2|⊕⊕◯◯)

2.5 Evidence

Because the normal level of "prepagetic" bone turnover will be unknown for most patients, the usual aim is to reduce turnover values into the lower half of the reference range because this increases the probability that individual patient normal values will have been achieved. After zoledronate treatment, achieving total ALP in the lower half of the normal range at 6 months was associated with a 6-year risk of losing therapeutic response of <10% (66). Duration of biochemical remission correlates inversely with the minimum post-treatment value and also with the short-term reduction in turnover (79). Because the duration of biochemical remission is strongly determined by the nadir value achieved by treatment (79–81), it seems reasonable to suppose, despite a lack of objective evidence, that long-term complications such as fracture, deformity, and degenerative joint disease might be prevented or reduced by long-term normalization of bone turnover.

2.5 Values and preferences

This recommendation places a higher value on experience drawn from early intervention in other diseases that shows a reduction in the risk of future complications and a lower value on negative trials in Paget's disease where late intervention has proved ineffective. However, effective therapy halts disease progression as assessed radiologically, histologically, and biochemically.

Relapse and retreatment

2.6 We recommend that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms. (1|⊕⊕⊕◯)

2.6 Evidence

The frequency of biochemical monitoring will depend on the therapeutic agent that the patient receives. The prolonged response after zoledronate treatment can be assessed every 1 to 2 years after normal bone turnover is demonstrated (66). With less-effective drugs, every 6 to 12 months would be appropriate (66).

Once treatment has been completed, there is a tendency for bone turnover to slowly return to baseline, and the rate of change is inversely related to bisphosphonate potency (inhibition of osteoclasts and retention in bone). Measurements can be made at approximately 6- to 12-month intervals with drugs of lesser potency and at 1- to 2-year intervals during the prolonged remission seen with zoledronate. Recurrence of bone pain in the absence of an increase in bone turnover is unusual; because it may be due to other causes such as degenerative joint disease, it is therefore an insensitive indicator of relapse.

Monostotic Paget's disease

2.7 We suggest that P1NP or BSAP and βCTx or NTx should be used for assessing the activity of untreated monostotic Paget's disease, although these may be normal when evidence of disease activity is still clearly demonstrated on scintigraphy. (2|⊕⊕◯◯)

2.7 Evidence

Limited disease activity presents a challenge to biochemical monitoring, and BSAP seems to be the most sensitive marker in that it was increased in 60% of patients with limited disease activity/extent, although total ALP was normal (46). However, in this study P1NP, βCTX, and NTX assays were not available for comparison. Either βCTx or NTx with a bone formation marker should provide the best chance of providing biochemical evidence of responsiveness to treatment.

2.7 Remarks

The implications for the use of biochemical diagnostic tests are more challenging but are similar to their use in polyostotic disease. If baseline biochemical tests are normal, a follow-up radionucleotide scan may determine a significant response to treatment.

2.7 Values and preferences

The accurate assessment of disease activity places a high value on test specificity compared with cost and availability.

3.0 Management of the complications of Paget's disease

Hearing loss

3.1 We suggest treatment with a potent bisphosphonate to prevent worsening of a hearing deficit. (2|⊕⊕◯◯)

3.1 Evidence

Hearing loss is a potential complication of Paget's disease when the temporal bone is involved. It may be difficult in some cases to determine how much hearing loss is due to presbycusis and how much is due to Paget's disease of bone. There are no randomized, double-blind, placebo-controlled clinical trials in which the effect of antipagetic therapy is assessed on hearing loss in patients with Paget's disease of the temporal bone. In one study, calcitonin treatment appeared to prevent hearing loss as compared with an untreated control group over 5 to 8 years (82). Generally, patients who have been treated do not appear to have further rapid deterioration of hearing, but for the most part the hearing loss is not reversible (82). Cochlear implantation has been described, but experience is very limited (83).

Osteoarthritis

3.2a We suggest the use of analgesics as adjunctive therapy for mild-to-moderate joint pain due to joint cartilage deterioration in patients with Paget's disease adjacent to the painful joint. (2|⊕⊕◯◯)

3.2a Evidence

Paget's disease is often associated with joint pain, so general measures to address this, including analgesics, are appropriate. However, analgesics do not address the underlying disease process and are likely to ultimately prove to be inadequate as the joint damage or bone deformity progresses. For these reasons, analgesics should be regarded as adjunctive therapies only. It is conceivable that drug treatment of the Paget's disease may slow progression of the arthritic process.

3.2b For patients with severe osteoarthritis adjacent to Paget's disease of bone, we suggest bisphosphonate therapy before undergoing elective total joint replacement to prevent intraoperative hemorrhaging and postoperative loosening of the prosthesis. (2|⊕⊕◯◯)

3.2b Evidence

Osteoarthritis is a relatively common complication, particularly in weight-bearing joints such as the hip or knee, when the adjacent bones are affected by Paget's disease. In some cases, there is symptomatic improvement of bone pain in a joint region after treatment of the Paget's disease, but joint replacement is often required to restore function and relieve joint pain. In such cases, the presence of Paget's disease can make the surgery more challenging (84, 85). Because there is increased blood flow to areas of active Paget's disease, preoperative therapy should reduce blood flow and lessen the chance of hemorrhage. Reduction of osteoclast activity should also reduce the chance of loosening of the prosthesis and prevent more rapid progression of Paget's disease, as has been reported after orthopedic surgery (86). Heterotopic bone formation is a rare complication after surgery that may require specific intervention (87). If surgery is required in the near future, an iv bisphosphonate should be given 1 to 2 months before the operation if possible. An oral bisphosphonate could be used if surgery can be delayed for 3 to 4 months. A high dose of etidronate should never be used in such cases because it may increase fracture risk and impair healing due to impairment of mineralization (88).

Bowing of lower extremity

3.3 We suggest treatment with a potent bisphosphonate before elective surgery for patients who require an osteotomy to correct severe bowing of the lower extremity associated with impaired ambulation and/or severe joint pain. (2|⊕⊕◯◯)

3.3 Evidence

Although there are no controlled trials, it is likely that reducing the blood flow to a tibia or femur that requires straightening will improve the surgical outcome, decrease the possibility of nonunion, and prevent acceleration of the pagetic activity that has been observed after surgery in untreated patients (89). The activity of osteoclasts has been shown to decrease dramatically 24 to 48 hours after iv bisphosphonate therapy (90). As in the case of joint replacements, either an iv bisphosphonate should be given 1 to 2 months in advance or an oral bisphosphonate should be given 3 to 4 months in advance.

Paralysis

3.4 In cases of paraplegia associated with Paget's disease of the spine, we suggest immediate treatment with a potent iv bisphosphonate associated with neurosurgical consultation. Surgical intervention may not be necessary after effective medical treatment unless there is severe structural damage. (2|⊕⊕◯◯)

3.4 Evidence

Most patients with paralysis recover well after medical treatment only (91, 92), presumably due to correction of ischemia due to vascular "steal." However, if there is severe structural damage, surgery may well be required, although the surgical outcome is not always optimal.

Neoplasms

3.5 We suggest that patients with osteosarcoma or a giant cell tumor be evaluated by an orthopedic surgeon (ungraded recommendation). If surgery is planned, we suggest pretreatment with a potent bisphosphonate to reduce bleeding from adjacent pagetic bone. (2|⊕⊕◯◯)

3.5 Evidence

Osteosarcoma is a complication that is fortunately rare. These tumors may arise in pagetic bone because of the proliferation of osteoblasts. Outcomes of treatment have generally been poor, as widely described in the literature (16). Notably, in the modern era with highly effective antipagetic drugs, there seem to be fewer cases of pagetic osteosarcoma. Giant cell tumors, usually benign, are described in a small number of patients with Paget's disease of bone and have responded to radiation, but they are usually treated surgically. Pretreatment with high-dose dexamethasone has been reported to reduce tumor size in two patients (93). Denosumab may shrink giant cell tumors in patients without Paget's disease (94). In 2013 it was approved by the Food and Drug Administration for

the treatment of patients who have unresectable tumors or in whom surgical resection is likely to result in severe morbidity. There is no specification regarding its use in nonpagetic vs pagetic tumors. The recommended dose is 120 mg sc every 4 weeks. Calcium and vitamin D should be taken to prevent or treat hypocalcemia.

Congestive heart failure

3.6 We suggest treatment with a bisphosphonate in patients with Paget's disease and congestive heart failure. (2|⊕⊕◯◯)

3.6 Evidence

Increased cardiac output and low peripheral vascular resistance are present in patients with extensive skeletal involvement (95). High output cardiac failure may occur in such patients, but it is not very common. The effects of treatment on heart failure have not been systematically studied, but high cardiac output may be reduced with effective therapy (96).

Appendix

Discriminatory value of biochemical markers

Analytical (interassay coefficient) and biological (within subject) variation determines the choice of marker used to monitor treatment, and the least significant change (LSC), derived from these measurements, indicates whether two sequential measurements reflect a true biological difference (46, 97). Measurements on automated platforms perform better than the manual methods, whereas serum markers show lower within-subject biological variability than those in urine. The best marker is one that shows a substantial decrease with treatment when expressed as a ratio to the LSC. BSAP, P1NP, and NTx show the largest ratio of change/LSC ratio during antiresorptive treatment (40, 98).

Total ALP is a cost-effective test for routine use to monitor the response to treatment (41, 36). The use of an additional marker to provide a baseline and assessment of the response to treatment (*Section 3.5*) will depend on patient characteristics, local availability, and cost.

Evaluation of marker sensitivity during treatment of monostotic disease is best achieved by expressing the decrease in turnover as a ratio to the LSC for that particular marker in a normal subject. In this respect, BSAP shows a much better response than total ALP, although P1NP may also be useful for monitoring with a ratio of >2. Current resorption markers seem to be less useful, with only NTx having a ratio >1, whereas hydroxyproline, serum CTx, and urinary CTx all had ratios less than unity (98). Although αCTx may change more than other markers in response to treatment (44), its lack of availability is a major disadvantage.

Treatment-induced changes in biochemical measurements, often within the reference range, cannot be evaluated without an understanding of the precision and reproducibility of the measurement.

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