PAGET’S DISEASE

Joseph R. Tucci, MD, FACP, FACE
Director, Division of Endocrinology and Metabolism, Roger Williams Medical Center; Professor of Medicine, Boston University School of Medicine; Adjunct Professor of Medicine, The Warren Alpert School of Medicine at Brown University

Participant in Alendronate, Risedronate, and Zoledronic Acid Therapy Studies of Paget’s Disease
22-Year Evolution of a Skeletal Disease in Patient from North of England (1877)

- First seen at age 46 years
- Mis-shapen shins
- Enlargement and bowing of the right femur
- Increasing skull circumference
- Spine curvature and rigidity
- Height decrease from 73 to 69 inches
- Simian-like posture
- Decreased hearing
- Mitral valve insufficiency
- Finally, development of pain and mass in proximal left forearm and, in 3 months, emaciation, pleural effusion and death at age 68 years from osteogenic sarcoma
Paget’s Disease
Definition

Localized bone disorder of one or more bones characterized by increased osteoclast number, size and activity with disordered bone resorption and formation and a disorganized mosaic of woven and lamellar bone at affected skeletal site(s) resulting in expanded bone with increased vascularity and susceptibility to deformity and fracture.
Clinical Vignette
Natural History of Untreated Paget's Disease of the Tibia

ETHEL S. SIRIV and FRIEDA FELDMAN


B 1964 1976 1987
Fig. 16. Radiograph of the tibia of man aged 60 years showing typical appearance of fracture in Paget's disease.

Fig. 17. Lateral view of tibia in same patient.
The fourth digit on the left is longer than normal owing to Paget's disease involving the proximal phalanx. Compare with the uninvolved hand on the right.
FIGURE 32
Paget’s disease in an isolated thoracic vertebra.
Epidemiology

- 3 million cases in USA
- Up to 3% over 50 years of age
- Up to 10% by age 80 to 90 years of age
- Mean age at diagnosis: 58 years
- Males > females
- Greater prevalence in rural rather than in urban areas
- Family history positive in up to 40% of cases
- Most common among Anglosaxons
- Frequent in North America, Europe (with exception of Scandinavian countries and Ireland), Australia, and New Zealand
- Rare in China, Japan, India, and Sub-Saharan Africa
Decreasing Prevalence of Paget’s Disease

• Data suggest a decrease in frequency and severity of PD in Great Britain and New Zealand between the 1970s and 1990s

• On the other hand, in 2006 an increase in the severity of familial and sporadic PD was reported in southern Italy
Etiology - Genetic Data

- 15 to 40% of patients with PD have a positive family history
- Those with a family history of PD have a 7 fold increased risk of the disease
- Data are consistent with an autosomal disorder with variable penetrance
- Several genetic variants have been identified, the most important- mutations in sequestosome 1 (SQSTM1) gene in up to 50% of familial and 5 to 15% of sporadic cases of PD. Rare in those without PD
- SQSTM1 gene encodes a protein, p62, that is involved in RANK activation; mutations of p62 may be responsible for abnormal RANK signaling and disordered osteoclast activity
- The majority of patients with PD do not carry such mutations
- Recent in vitro and in vivo studies suggest that SQSTM1 mutations are predisposing rather than causative
Etiology - Slow Virus Infection? No Clearcut Conclusions Yet!

- Measles and other paramyxoviruses including canine distemper virus have been implicated.
- Inclusions found in the nucleus and cytoplasm of pagetic osteoclasts resemble nucleocapsids of paramyxoviruses.
- Measles and canine distemper viral transcripts found in pagetic osteoclasts and measles transcripts also detected in peripheral monocytes.
- Other data do not confirm presence of viral transcripts in pagetic bone, blood cells, or bone marrow.
- A virus has not been isolated from pagetic bone or peripheral blood cells and no increase in circulating antibody titers to canine distemper or measles virus has been reported.
Pathogenesis

Neither the genetic nor the viral “etiology” explains the varying clinical phenotype developing generally after age 50 years, occurring in one or more bones with no tendency to “metastasize” and with no altered bone turnover in uninvolved bone. As a result there remains a question of other environmental factor(s) or toxin(s)
Histopathology

- Both bone resorption and formation occur at an increased rate in pagetic bone, but the major pathology is in the numerous osteoclasts that can be increased up to 100-fold.
- Reflecting its increased resorptive activity, the pagetic osteoclast is large and hypernucleated.
- Apoptosis of pagetic osteoclasts may be retarded.
- Evidence also of abnormal activity of marrow stromal cells and osteoblasts with resultant mosaic pattern of woven and lamellar bone.
- Bone marrow infiltrated by connective tissue and increased vascularization of involved bone.
- Ultimately, bone may become less metabolically active, less hypercellular, and more sclerotic in keeping with inactive or burned-out PD.
Other “Osteoclast” Findings

• Available data support a role for an abnormal bone microenvironment in promoting osteoclastogenesis, altered osteoclast morphology, activity, and lifespan.
• Pagetic osteoclast precursors are hypersensitive to RANKL and 1,25-OHD.
• Osteoclast precursors with an increase in D-binding protein may in part explain an increased sensitivity to 1,25-OHD.
Presenting Features

- Incidental X-ray finding
- Increased serum alkaline phosphatase
- Bone and/or joint pain
- Fracture
- Bone deformity
- Neurologic symptoms
Skeletal Involvement

- 75% of patients - polyostotic
- Common sites
  - Pelvis
  - Spine, especially lumbosacral
  - Femur
  - Skull
  - Tibia
- Rare sites
  - Ribs
  - Fibula
  - Carpal, tarsal and phalangeal bones
Musculoskeletal Complications of Paget’s Disease

- Skeletal pain - periosteal stretching, blood flow, fissure fracture
- Skeletal deformities
- Fractures with a nonunion rate of 10%
- Secondary osteoarthritis
- Sarcoma
Neurologic Complications of Paget’s Disease

- Hearing deficit (sensory and/or conductive; cochlear)
- Other cranial nerve deficits
- Mottled retinal degeneration; angioid streaks
- Basilar impression, invagination
- Hydrocephalus
- Myelopathy
- Radicular neuropathies
- Spinal stenosis
- Spinal vascular steal syndrome
Cardiovascular System and Paget’s Disease

- Increased cardiac output with >35% skeletal involvement
- Congestive heart failure
- Generalized atherosclerosis
- Aortic valve calcification
- Endocardial calcification
Skeletal blood flow measurements in normal subjects and in untreated patients with Paget's disease. Note the logarithmic scale. (From Woolson et al., 1981.)
Neoplastic Complications of Paget’s Disease

• Sarcoma
  – Osteosarcoma
  – Chondrosarcoma
  – Fibrosarcoma

• Giant-cell tumor or osteoclastoma (responsive to dexamethasone)
Metabolic Concomitants of Paget’s Disease

- Hypercalcemia and hypercalciuria with immobilization
- Hyperparathyroidism
  - Primary - most likely coincidental
  - Secondary - 15-20% prevalence due to decreased vitamin D levels and/or renal insufficiency
Diagnosis of Paget’s Disease

- Serum alkaline phosphatase
- Bone specific alkaline phosphatase
- Bone scan
- X-rays
- Urinary N-telopeptide or plasma C-telopeptide
- Bone biopsy
Radiology

- Enlargement and anterolateral bowing of a long bone.
- Coarse trabecular thickening with obliteration of the bone medulla.
- Osteolysis eventually replaced by osteosclerosis usually begins in the epiphyseal and metaphyseal regions.
- Advancing lytic wedge ("blade of grass" appearance) in long bone; advances 0.7-1.0 cm/year.
- Rarity of involvement of new skeletal sites!
Radiology (Cont’d)

- Incomplete, small transverse fissures in the cortex along the convex side of the bowed long bones.
- Differential diagnosis of Paget’s vs. metastatic disease. In early stages, difficult to make the diagnosis by X-ray because of the chaotic underlying architecture of pagetic bone.
- Discrete oval or round areas in the skull (osteoporosis circumscripta) that may coalesce over a period of years. Malignancies generally produce small and numerous osteolytic foci that do not coalesce.
Paget’s Disease
Indications for Therapy

• Extensive disease
• Pagetic pain
• Pagetic fracture
• Pagetic deformity
• Neurologic complications
• Area of critical involvement
• High output congestive heart failure
• Sarcoma
Therapy For An Area Of Critical Involvement???

- Even in an asymptomatic patient progression of pagetic activity has been well established!
- 2001 - Tiegs: question is whether to treat or not
- 2001 - Lyles et al: reduction in complications and morbidity now possible
- 2002 - Papapoulos: indications for therapy include prevention of complications
- 2006 - Siris et al: treat to prevent future complications
- 2008 - Ralston et al: no firm evidence for therapeutic prevention of complications
- 2010 - Langston et al: question as to clinical benefits of therapy
- 2011 - Reid, Hosking: now, presumptive evidence that therapy will prevent complications
- 2014 - Tiegs: until we have better data, decision to treat should be based on clinical judgment and patient preference
Therapy For An Area Of Critical Involvement (Cont)

- 2013- Bone Research Society of the United Kingdom Guidelines: treatment of asymptomatic patients is not recommended because treatment has not been shown to prevent complications.

- 2014- Endocrine Society Clinical Practice Guidelines- “We suggest treatment with a bisphosphonate for most patients with active Paget’s disease who are at risk for future complications. There has been a broad consensus that therapy should be offered to patients with active disease who are either symptomatic or at significant risk of future complications.”
Pharmacotherapy of Paget’s Disease

- Calcitonin
  - Salmon
- Bisphosphonates
  - Etidronate
  - Pamidronate
  - Alendronate
  - Tiludronate
  - Risedronate
  - Zoledronate
Chronic Treatment With Salmon Calcitonin

- Bone turnover
- Normal range

Calcitonin treatment:
- Resistance
- Plateau response
- Primary nonresponse

Control

From Hosking, 1995
Calcitonin

- Uninterrupted therapy can continue to suppress bone turnover in some patients
- It can continue to alleviate pagetic pain and some neurologic deficits and decrease pagetic bone vascularity with a positive effect on lytic lesions and improvement in bone histopathology
- Therapy generally limited to patients intolerant to bisphosphonates or to patients with renal insufficiency
- Adverse effects include nausea, flushing, abdominal discomfort, and diarrhea
Bisphosphonates

- Treatment of choice for active Paget’s disease
- Bisphosphonates are analogues of pyrophosphates in which a carbon atom has replaced the oxygen atom resulting in compounds that are stable and resistant to enzymatic hydrolysis
- Non-nitrogen containing bisphosphonates such as etidronate, tiludronate, and clodronate inhibit osteoclastic activity through formation of cytotoxic ATP analogues
- Nitrogen-containing bisphosphonates such as alendronate, risedronate, pamidronate, and zoledronate inhibit osteoclastic activity through inhibition of farnesyl pyrophosphate synthase of the mevalonate pathway
- Therapy decreases bone turnover, alleviates bone pain, promotes healing of lytic lesions, and can restore normal bone histology
- Potency varies from a value of 1 for etidronate, 10 for tiludronate, 100 for pamidronate, 1000 for alendronate, >1000 for risedronate, and 10,000 for zoledronate
- Adverse effects include myalgia, bone pain, and with oral intake reflux, abdominal pain, nausea, vomiting, and diarrhea; acute phase reaction with first doses especially parenteral; uveitis a rare complication
Calcium And Vitamin D

- Inhibition of osteoclastic activity with the more potent aminobisphosphonates, pamidronate, alendronate, risedronate, and zoledronate can result in hypocalcemia
- Inadequate dietary calcium intake and limited sun exposure and vitamin D intake are common in the elderly and in those with PD
- Optimization of calcium intake and vitamin D status should be routinely recommended and discussed with patients prior to, during, and following bisphosphonate therapy
### SAP Response to 180 mg Pamidronate Treatment in 80 Patients with Paget’s Disease

(Tucci, Bontha. Endocr Pract, 2001;7:423-429)

<table>
<thead>
<tr>
<th>Baseline Alkaline Phosphatase</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3x ULN</td>
<td>86%</td>
</tr>
<tr>
<td>≥ 3-6x ULN</td>
<td>38%</td>
</tr>
<tr>
<td>≥ 6x ULN</td>
<td>12%</td>
</tr>
</tbody>
</table>

Duration of remissions from 4 to 48 mos
Mean 16 mos and median 15 mos
Alendronate

\[
\begin{align*}
\text{NH}_2 \\
\text{(CH}_2\text{)}_3 \\
\text{O}^- \\
\text{O} \\
\text{O}^- \\
\text{O}^- \\
\text{P} \\
\text{C} \\
\text{OH} \\
\text{O}^- \\
\text{O}^- \\
\end{align*}
\]
MEAN PERCENT CHANGE FROM BASELINE IN SERUM ALKALINE PHOSPHATASE BY TIMEPOINT

- Mean + S.E.
- Mean - S.E.
- Geometric Mean

At Month 6, p < 0.001
MEAN PERCENT CHANGE FROM BASELINE IN URINARY DEOXYPYRIDINOLINE BY TIMEPOINT

Percent Change from Baseline vs Time in Months

- Mean 
- Mean + S.E. 
- Mean - S.E. 
- Geometric Mean

- Alendronate (○)
- Etidronate (△)

At Month 6, p < 0.01
TABLE 2. Percentage of patients who were defined as responders (decrease ≥60% from baseline or normalization of serum alkaline phosphatase) and normalizers (patients who normalized their alkaline phosphatase)

<table>
<thead>
<tr>
<th>Time from start of treatment</th>
<th>Alendronate (n = 41)</th>
<th>Etidronate (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>2.4</td>
<td>0.0</td>
</tr>
<tr>
<td>3 months</td>
<td>63.4</td>
<td>17.0</td>
</tr>
<tr>
<td>6 months</td>
<td>87.8</td>
<td>29.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normalizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3 months</td>
<td>26.8</td>
<td>10.6</td>
</tr>
<tr>
<td>6 months</td>
<td>63.4</td>
<td>17.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.001 (alendronate vs. etidronate).
Risedronate
Study Design

Double-blind, active-control study
Baseline ALP at least twice the upper limit of normal

Treatment

Risedronate 30 mg/day

<table>
<thead>
<tr>
<th>Tx</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>360</td>
</tr>
</tbody>
</table>

Etidronate 400 mg/day

<table>
<thead>
<tr>
<th>Tx</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>360</td>
</tr>
</tbody>
</table>

Duration of Study (Days)
Figure 1: Mean Percent Change from Baseline in Serum Alkaline Phosphatase by Visit

Graph showing changes in serum alkaline phosphatase levels over time for 400 mg Diclofenac and 30 mg Risedronate treatments.
## Alkaline Phosphatase Response Data

<table>
<thead>
<tr>
<th>Response category</th>
<th>Etidronate 400 mg (n = 60)</th>
<th>Risedronate 30 mg (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% decrease in AP</td>
<td>7 (11.7%)</td>
<td>0</td>
</tr>
<tr>
<td>≥ 10%, but &lt; 30% decrease in AP</td>
<td>9 (15.0%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>≥ 30%, but &lt; 50% decrease in AP</td>
<td>14 (23.3%)</td>
<td>3 (5.0%)</td>
</tr>
<tr>
<td>≥ 50%, but &lt; 75% decrease in AP</td>
<td>16 (26.7%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>≥ 75% decrease in AP</td>
<td>14 (23.3%)</td>
<td>51 (85.0%)</td>
</tr>
<tr>
<td>Patients normalizing AP</td>
<td>9 (15.0%)</td>
<td>44 (73.3%)*</td>
</tr>
<tr>
<td>Median days to normalization</td>
<td>&gt;360</td>
<td>91*</td>
</tr>
<tr>
<td>Patients relapsing#</td>
<td>8 (15.1%)</td>
<td>2 (3.3%)</td>
</tr>
</tbody>
</table>

* \( p < 0.001 \)

# Relapse was defined as ≥ 50% increase in AP from the nadir, and reaching a 2x upper limit of normal
Zoledronate

\[
\begin{align*}
\text{OH} & \quad \text{P} & \quad \text{C} & \quad \text{P} & \quad \text{O} \\
\text{O}^{-} & \quad \text{O} & \quad \text{O}^{-} & \quad \text{O}^{-} & \quad \text{O}^{-} \\
\text{O}^{-} & \quad \text{CH}_2 & \quad \text{N} & \quad \text{N} & \\
\text{O}^{-} & \quad \text{O}^{-} & \quad \text{O}^{-} & \quad \text{O}^{-} & \\
\end{align*}
\]
Comparison of a Single Infusion of 5 mg of ZA Compared with Risedronate 30 mg/day for 60 days (Reid et al. NEJM 2005;353:898-908)

- International study in 10 countries and 76 centers involving 182 patients in the ZA group and 175 in the risedronate group
- Primary efficacy end point - rate of therapeutic response at 6 months defined as normalization of serum alkaline phosphatase or reduction of at least 75% of excess alkaline phosphatase
- Normalization of alkaline phosphatase occurred in 89% of patients treated with ZA and in 58% of patients treated with risedronate
- ZA therapy was associated with a shorter median time to a therapeutic response as compared with risedronate
- Over 6 months - loss of therapeutic response in 1/113 patients in ZA group vs 21/82 patients in the risedronate group
- Quality of life survey (36 items) - a significant increase at 3 and 6 months with ZA vs risedronate
- Adverse events - hypocalcemia in first 2 weeks in 8 patients in the ZA group (6 asymptomatic) and one with severe hypocalcemia in the risedronate group
## Therapeutic Response

<table>
<thead>
<tr>
<th>Visit Day</th>
<th>Zoledronic Acid</th>
<th>Risedronate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N Proportion</td>
<td>n/N Proportion</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2/81 0.02</td>
<td>0/84 0.00</td>
<td>N/A</td>
</tr>
<tr>
<td>28</td>
<td>21/88 0.24</td>
<td>1/88 0.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>63</td>
<td>78/88 0.89</td>
<td>42/89 0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>91</td>
<td>80/88 0.91</td>
<td>59/89 0.66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>182</td>
<td>84/88 0.95</td>
<td>67/89 0.75</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
SAP Normalization Over Time

% Patients

* p<0.001

Day

Zoledronic Acid

Risedronate
6½ Year Followup Study of Responders

- Objectives: monitoring longevity of therapeutic responses by documenting relapse rates (return of ALP to 20% of pretreatment values) or loss of a therapeutic response; also, quality of life scores
- Relapse
  - ZA therapy 1/152 (0.7%)  RIS therapy 23/115 (20%)  p< .001
- Loss of therapeutic response
  - ZA therapy 19 (12.5%)  RIS therapy 71 (62%)  p<.001
- Data demonstrate an unprecedented duration of remission following therapy with ZA
- Also quality of life scores were more positive in the ZA group
Efficacy and Safety of Intravenous ZA in the Treatment of Patients with Resistant PD of Bone (Tucci. Endocr Pract 2015;21:1111-1116)

- Primary objective: to determine frequency of therapeutic response defined by normalization of alkaline phosphatase or a reduction of at least 75% in excess alkaline phosphatase following an infusion of ZA in 14 patients who had not experienced a remission or had a relapse within a year of therapy with pamidronate, alendronate, and/or risedronate.

- Serum alkaline phosphatase and urine NTx were measured at 1, 3, 6, 9, and 12 months post infusion and after 12 months patients in remission had these measurements for up to 60 months.

- Remissions were induced in 13 patients and were more prolonged than prior remissions of less than 12 months, 2 for 36 mos, 2 for 48 mos, and 2 for 60 mos.

- The lack of remission in 1 patient despite 2 courses of therapy is evidence of a continuing challenge for some patients with a more resistant form of PD.
Randomized Trial of Intensive Bisphosphonate Treatment Versus Symptomatic Management in Paget’s Disease of Bone (Langston et al. JBMR 2010;25:20-31)

• Study initially of 1324 patients with Paget’s disease comparing the effect of symptomatic treatment with bisphosphonates vs intensive group that was treated to reduce and maintain alkaline phosphatase levels in the normal range.

• Conclusions- no clinical advantage of intensive therapy as opposed to symptom driven therapy; neither approach strongly had significant beneficial impact on pain or quality of life

• Note- this was an early study that did not include therapy with ZA

• Response by Reid et al JBMR 25, 1463-1464, 2010- though randomized trials have not been conducted, demonstration of sustained biochemical and histological normalization with healing of radiologic lesions makes it highly probable that deformities that can result from such lesions will be averted
Durability of Response to ZA Treatment and Competing Mortality in Paget's Disease of Bone (Cundy et al. JBMR 2017;32:753-756)

- A marked secular trend in recent decades of patients with PD presenting at a greater age with less extensive disease
- Study of 108 patients treated with ZA at mean age of 76 yrs
- By 9 years only 14% had a biochemical relapse defined as a P1NP value >80 ug/L (ULN)
- The mortality rate was greater than the relapse rate; by 10 years more than half the cohort had died
- Conclusion: for the majority of older patients with PD a single infusion of ZA will provide disease suppression for the remainder of their lives
Therapeutic Comments

• All the aminobisphosphonates are potent and effective agents in Paget’s disease but zoledronic acid and risedronate appear to be the most effective.

• A single infusion of zoledronic acid is the most potent therapy which in most cases can result in a rapid and more sustained remission.

• Clinical and biochemical followup at 3, 4, or 6 monthly intervals and in patients with lytic lesions a repeat X-ray one year after therapy.

• Salmon calcitonin can be used in patients intolerant to bisphosphonates or in those with renal insufficiency.
Paget’s Disease – The Future

- Possible to suppress disease activity in most patients
- Results will often be long lasting
- “Maintenance” therapy is not required
- Progression of Paget’s disease may be preventable if treated early
- However, even today there are patients who are not responsive to current therapy
- Last comment, “at present the vast majority of patients are neither diagnosed nor treated” - Maricic, 2007