

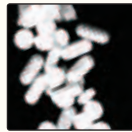
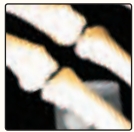
# OSTEOPOROSIS



## INTRODUCTION

The number of osteoporosis patients continues to rise worldwide. New drugs have come onto the market to treat or prevent the disease, but not all the treatments are suitable for everyone, and sometimes combining or alternating drugs brings better results. Research is clarifying aspects of existing drugs and is offering new therapeutic avenues, holding out hope for even more effective ways to combat this crippling disease.

# THERAPEUTICS: BISPHOSPHONATES AND BEYOND



## 3 perspectives

### BASIC RESEARCHER PERSPECTIVE

► By David B. Burr, Ph.D.

Dr. Burr is professor and chair of the Department of Anatomy and Cell Biology at Indiana University School of Medicine in Indianapolis.



#### Highlights

- BPs work through multiple signaling pathways to reduce the number of resorption sites and erosion depth.
- BPs preserve bone mass, but they increase bone brittleness by allowing accumulation of advanced glycation end-products.
- BPs alter tissue, increasing initiation of micro-damage and preventing its repair by suppressing remodeling.
- Newer agents work through the immune system either by interfering with ligand-receptor systems to prevent activation of osteoclastic resorption (denosumab), or by interrupting the natural down-regulation of bone formation (anti-sclerostin antibody).

Substantial basic research has been done in animal models over the past 40 years to understand how bisphosphonates (BPs) work in bone—from the molecular to the tissue level. Studies intended to distinguish the effects of various BPs continue, but we have a good understanding of

their speed of onset and withdrawal, their potencies, their effects in fracture healing, and their efficacy in sequential or combination treatments.

#### Mechanism of Action

BPs prevent osteoclast activation by inducing apoptosis via interruption of the mevalonate pathway. They inhibit both farnesyl diphosphonate synthase and GGPPS (geranylgeranyl diphosphate synthase), blocking prenylation of small GTPases such as Ras, Rho, Rac, and Rap, and cell-survival signaling pathways. Interaction of these GTPases with the cell membrane down-regulates the Akt and ERK1/2 signaling pathways, causing cytochrome c release and, eventually, the activation of caspases. BPs can also induce cell cycle arrest in the S phase, an effect sometimes accompanied by apoptosis via caspase activation. This action suppresses overall remodeling of bone, reducing both the number and depth of erosions caused by normally functioning osteoclasts.<sup>1</sup>

BPs may act via many signaling pathways, some of which are specific to individual BPs. These include:

- Altering key apoptotic proteins, specifically increasing Bax and decreasing Bcl-2.
- Activating the mitochondrial pathway via translocation of apoptosis-inducing factor.
- Inhibiting mitochondrial adenine nucleotide translocase (ANT), known to be involved in causing apoptosis.
- Inducing ApppI (an adenosine triphosphate analog), which triggers direct apoptosis through blockade of mitochondrial ANT.
- Inhibiting metalloproteinases necessary for proteolytic degradation of the extracellular matrix (ECM).
- Inhibiting cancer cell adhesion to the ECM, which down-regulates surface receptors (e.g., ICMA-1 and VCAM-1) and prevents cancer cells spreading at lower concentrations than those required to cause apoptosis.<sup>2, 3</sup>

## Effects on Bone

BPs effectively reduce fracture risk in postmenopausal women over periods of at least 10 years,<sup>4</sup> but preclinical studies demonstrate that they also negatively affect bone quality. Studies in dogs show a nearly 30% decline in material toughness (the normalized energy to fracture) over 3 years of treatment at doses that simulate those used in treating osteoporosis in postmenopausal women.<sup>5</sup> This creates a material more brittle than untreated bone, facilitating micro-damage, which, combined with the natural suppression of remodeling to repair it, significantly increases its burden in bone.<sup>5</sup> Micro-damage accumulation is likely a consequence of the increased brittleness and reduced toughness, not its cause. The change in bone tissue is more likely caused by larger accumulation of advanced glycation end-products, or AGEs.<sup>6,7</sup> These are the by-products of the formation of collagen cross-links by non-enzymatic processes, and naturally accumulate in bone as it ages. Under normal bone turnover rates, AGEs are prevented from accumulating to high levels. When bone turnover is suppressed, however, they can accumulate, and laboratory studies show them to be associated with increased brittleness.<sup>8</sup> The micro-damage accumulation, and possibly the build-up of AGEs in the tissue, can be reversed by teriparatide, a recombinant form of human parathyroid hormone (PTH) 1-34.<sup>9</sup>

## Newer Agents: The Future

Agents currently in development or under consideration by the U.S. Food and Drug Administration (FDA) work differently from BPs to reduce fractures. They hold substantial future promise. The binding of RANKL and its receptor RANK is what allows osteoclast activation and subsequent resorption. Denosumab, a fully human monoclonal RANKL antibody, prevents RANKL from binding to its receptor on the osteoclast—a fundamentally different approach to preventing bone loss than that of BPs.<sup>10</sup> Denosumab has the advantage of being fully reversible in a short time, if necessary, whereas BPs are embedded in bone and can remain there for long periods. Denosumab is more potent than oral BPs, but probably somewhat less so than the current generation of intravenous BPs.

An anti-sclerostin antibody is also currently under development. Sclerostin is a negative regulator of the Wnt system in bone, so it reduces how much bone formation can occur. Neutralizing sclerostin with such an antibody will increase Wnt signaling, leading to higher net bone formation and strength.<sup>11</sup> BPs and denosumab are considered to be anti-catabolic agents because they suppress remodeling, thus preventing bone loss. By contrast, sclerostin, like teriparatide, is a potential anabolic treatment, allowing formation to exceed resorption at any remodeling site. This distinction is especially important for patients with very low bone mass, in whom the potential to increase formation may reestablish a more normal bone mineral density.

## Conclusion

BPs have been the standard of care for treating osteo-

porosis for the past 15 years. They are very effective at reducing fracture risk, but over prolonged periods, their negative impact on tissue quality may make them less so. Newer agents that work immunologically show great promise for preventing bone loss and even increasing bone mass.

## CLINICAL RESEARCHER PERSPECTIVE

► By Tamara J. Vokes, M.D.

Dr. Vokes is professor of endocrinology at the University of Chicago in Ill.



### Highlights

- Current therapeutic agents for osteoporosis differ in potency, mechanism of action, and duration of effect, allowing individualized treatment approaches.
- FDA approval of osteoporosis agents requires documented fracture reduction in placebo-controlled trials, which are costly and require many subjects. Anti-fracture efficacy is consequently known only for single agents and not their comparisons and combinations.
- Bone density changes underestimate the improvement in bone strength and fracture reduction observed in clinical trials.
- BPs reduce teriparatide's anabolic effect. Although this may not be true for estrogen and its analogs, combination therapies are not routinely employed.
- The theoretical goal of simultaneously reducing bone resorption and stimulating bone formation has not been realized with current therapies, possibly explaining why some patients continue to fracture.
- Further reducing fracture incidence requires novel agents with greater efficacy and lower cost, efforts to improve recognition of osteoporosis, and therapeutic compliance and persistence.

FDA approval of osteoporosis therapies requires demonstrated fracture reduction in a placebo-controlled trial. Because fractures are relatively infrequent, such trials are costly and need many participants. Using bone mineral density (BMD) as a surrogate for bone strength might allow smaller trials to compare different drugs or their combinations. In placebo-controlled trials of single agents, however, the reduction in fracture risk is considerably greater than accounted for by the increases in BMD.<sup>1</sup> Care should therefore be exercised when estimating anti-fracture efficacy from BMD changes.

## Antiresorptive (Anticatabolic) Agents

Four BPs—alendronate, risedronate, zoledronic acid, and ibandronate—are FDA-approved. Each reduces the relative risk of new vertebral fractures (by 40%–70%).<sup>2</sup> The first

three also cut the risk of non-vertebral (25%–35%) and hip fractures (about 40%).<sup>2</sup> Because BPs are incorporated into the bone mineral, their antiresorptive effect is long lasting, which has led to less frequent dosing regimens<sup>2</sup> and consideration of a “drug holiday” after 5 years, as described in the clinical section below.

Estrogen is approved for preventing osteoporosis. The Women’s Health Initiative trial demonstrated significant reduction in the risk of hip (34%), vertebral (34%), and other osteoporotic fractures (23%).<sup>3</sup> Raloxifene, the only selective estrogen receptor modulator (SERM) approved for osteoporosis, curbed vertebral fractures (by 30%–50%) but not non-vertebral fractures.<sup>4</sup> Raloxifene’s effect on bone density and markers is less than that of estrogen,<sup>5</sup> but raloxifene reduces breast cancer risk and thus may be particularly attractive for some women. Although alendronate (70 mg/week) and estrogen (0.625 mg of conjugated estrogen) yield similar BMD increases, bone loss is rapid upon discontinuation of estrogen whereas bone mass is preserved after stopping a BP.<sup>6</sup> Therefore, women with fracture risk should receive another osteoporosis therapy when they discontinue estrogen or SERM.

Denosumab is likely to receive FDA approval in the near future. A potent antiresorptive agent, at a 60-mg dose given subcutaneously every 6 months, it reduces the relative risk of vertebral (by 68%), hip (40%), and non-vertebral (20%) fractures.<sup>7</sup> It produces slightly greater increases in bone mineral density (BMD) than alendronate but, in contrast to BPs, its effects dissipate quickly.

### Other Agents and Combinations

The only FDA-approved anabolic agent is teriparatide, given subcutaneously at 20 µg daily for 18–24 months. It reduced the relative risk of vertebral fractures (by 65%–69%) and non-vertebral fractures (by 35%–40%).<sup>8</sup> This pivotal teriparatide trial was terminated because early osteosarcoma developed in rats given a considerably higher dose at a young age. However, no evidence exists from clinical trials or post-marketing surveillance of increased osteosarcoma risk in postmenopausal women treated with teriparatide. The drug may be considered first-line therapy for patients with very high fracture risk or second-line therapy in those who fail BP treatment. It is a particularly attractive choice for glucocorticoid-induced osteoporosis, which is primarily due to dramatically reduced bone formation. In such patients, teriparatide is superior to alendronate not just in increasing BMD but also in preventing new vertebral fractures.<sup>9</sup> Bone loss is rapid when teriparatide is stopped, however, so it should be followed by an antiresorptive drug, usually a BP.

Strontium ranelate is an oral agent available in Europe, but not approved in the United States. Although believed to both increase bone formation *and* decrease bone resorption, its anti-fracture efficacy is no greater than that of BPs.<sup>10</sup>

Osteoporosis results from decreased bone formation and/or increased bone resorption, so combining an anabolic and an antiresorptive agent should theoretically have a synergistic effect. However, treatment-naïve patients show

greater BMD increase with teriparatide alone than patients pretreated with BPs or given a combination of both.<sup>11</sup> Although this has not been observed in patients given estrogen or raloxifene,<sup>12</sup> the data currently support sequential rather than concomitant use of anti-osteoporosis agents.

## CLINICAL PRACTITIONER PERSPECTIVE

► By David M. Slovik, M.D.



Dr. Slovik is associate professor of medicine at Harvard Medical School in Boston, Mass.

### Highlights

- Oral BPs are well-tolerated if taken appropriately.
- With intravenous zoledronic acid, acute phase symptoms are usually mild and less likely if the patient remains well-hydrated and pretreats with acetaminophen or other NSAIDs.
- Over-suppression of bone turnover can occur, but is relatively uncommon. Bone strength improves, BMD increases, and fracture risk decreases with BPs.
- ONJ is very uncommon and is seen primarily with intravenous BPs given in high doses to patients with cancer.
- Some, but not all, patients might benefit from a drug holiday after 5 years of treatment.

Since the first BP, alendronate, was approved in 1995, these agents have been first-line therapy for treating postmenopausal osteoporosis. The reported decreases in hip fracture rates result from multiple factors.<sup>1, 2</sup> Daily oral alendronate or risedronate and intravenous zoledronic acid reduce the risk of vertebral, non-vertebral, and hip fractures. Daily oral ibandronate lowers vertebral fracture incidence. Weekly and monthly oral preparations and intravenous ibandronate are similar to daily doses in increasing BMD. Intravenous zoledronic acid reduces vertebral fractures (70%), hip fractures (41%), and non-vertebral fractures (25%).<sup>3</sup>

### General Principles

Oral BPs are well-tolerated. They are poorly absorbed (< 1%) and should be taken on an empty stomach with 8 ounces of water. Patients should remain upright for 30 minutes (60 minutes for ibandronate), and avoid eating, drinking, or other medications during that time. Patients with Barrett’s esophagus should not take oral BPs.<sup>4</sup> The most common side effects are upper gastrointestinal symptoms. Occasionally muscle, bone, and joint pain can occur at any time during treatment.

With intravenous zoledronic acid, acute-phase symptoms include fever (16%), myalgia (10%), influenza-like illness (8%), headache (7%), and arthralgia (6.3%).<sup>3</sup> These effects are transient and believed to be due to inflammatory cytokines; they are most likely to occur with the first infusion, usually are mild and occur within the first 24 hours, and last 24–72 hours (occasionally longer). After the first infusion, any of these post-dose symptoms were seen in 32% of subjects; after the second, 7%; and after the third, 3%.<sup>3</sup> Patients should be adequately hydrated, may take acetaminophen or another non-steroidal anti-inflammatory (NSAID) agent, and should continue calcium and vitamin D supplements. Before the infusion, serum calcium, creatinine, and 25-OH vitamin D levels should be checked. BPs are not recommended when estimated creatinine clearance is below 30–35 ml/min. Patients with chronic kidney disease and creatinine clearance above these levels should have a reduced BP dose.

### Common Patient Concerns and Questions



**1. Will BPs weaken my bones?** Over-suppression of bone turnover with long-term BP use, resulting in delayed or absent fracture healing<sup>5</sup> and atypical subtrochanteric and femoral diaphyseal fractures,<sup>6</sup> has been reported. However, some studies, including a large cohort study in Denmark, sug-

gested these were more likely due to osteoporosis rather than alendronate treatment.<sup>7</sup> At this point, there is no clear connection between BP use and the risk of these atypical fractures, but more information is being gathered. Although over-suppression can occur, in reality it is very uncommon.

Bone strength is preserved, BMD increases, and fracture risk decreases with BPs.

- 2. Is there a link between BPs and atrial fibrillation?** In the HORIZON Pivotal Fracture Trial, a higher incidence of serious atrial fibrillation was seen in patients receiving zoledronic acid compared with placebo (1.3% vs. 0.5%).<sup>3</sup> However, no increase occurred in other zoledronic acid trials. Although a subsequent review of the Fracture Intervention Study (FIT) data with alendronate therapy showed a trend toward higher atrial fibrillation incidence, a large case-control study from Denmark found no increase. The data are thus conflicting and offer no definite association.<sup>8</sup>
- 3. What about the “jaw problem”?** Osteonecrosis of the jaw (ONJ) is the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care professional.<sup>9</sup> ONJ associated with BP therapy is seen primarily in cancer patients receiving intravenous BPs in doses much higher than those given for treating osteoporosis. In a large review, 94% of patients with ONJ on BP therapy had received IV BP for

cancer.<sup>10</sup> Whether the primary process (e.g., bone infection) is worsened by BPs or if the BPs have direct effects (e.g., inhibit bone resorption or are anti-angiogenic) is unclear. Trauma to the mouth is often the precipitating event. Patients should take care of major dental problems before starting BP treatment and practice good dental hygiene with regular follow-up.

#### 4. May I take a drug holiday?

No consensus exists on how long to continue BP therapy, but long-term treatment with alendronate (10 years) or risedronate (7 years) is well-tolerated. In the FIT Long-Term Extension (FLEX) study,<sup>11</sup> half the 1,099 postmenopausal women in the FIT trial were taken off alendronate after 5 years, whereas the other half remained on it for an additional 5 years. Women with severe osteoporosis were excluded. After 10 years, those who stopped alendronate experienced a gradual decline in BMD and increased bone turnover markers, but were still better than pretreatment. These patients showed no significant difference in morphometric vertebral fractures or non-vertebral fractures, but had a slightly higher risk for clinically observed vertebral fractures. Thus, a “drug holiday” after 5 years is reasonable for some women, but those at high risk for fracture should continue BP therapy.



### Other Therapies

PTH 1-34 is a well tolerated anabolic agent used for severe osteoporosis. In studies, PTH therapy increased BMD and curbed fractures (vertebral, 65%; non-vertebral, 35%).<sup>12</sup>

### Conclusion and What’s Ahead

BPs are generally safe, well tolerated, and effective agents to treat osteoporosis and reduce fractures. New agents working through different mechanisms to alter the bone-remodeling process will expand our options for treatment. Safe and effective agents are available to treat osteoporosis, but fractures remain a significant medical problem. Further reductions require development of even more efficacious therapeutic agents, better recognition of osteoporosis, lower therapy costs, and greater attention to compliance and persistence. ■

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