Overview of Bisphosphonates and Osteoporosis

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Program Overview:

To provide nurses, and pharmacists with an understanding of Osteoporosis and Bisphosphonates

OBJECTIVES:

After completing this program, pharmacists and nurses will be able to:

- Describe the remodeling process that occurs in bone
- Identify the current indications and doses of bisphosphonates for osteoporosis to their patients
- Outline the risk factors for osteoporotic fractures and current screening guidelines for patients at risk
Overview of Bisphosphonates and Osteoporosis

Karen von Koeckritz, Pharm.D.

Introduction

Osteoporosis has been called a silent disease. Patients often are unaware they have osteoporosis until a fracture occurs. A fracture due to osteoporosis may cause the patient, and possibly the patient’s family, great personal, medical and financial burdens. The risk of fractures due to osteoporosis can be decreased and sometimes eliminated with treatment. Osteopenia is a milder decrease in bone density than osteoporosis, and early detection can be an alert for proactive care. Bisphosphonates are the mainstay of osteoporosis treatment and prevention. The National Osteoporosis Foundation (NOF) published *The Clinician’s Guide to Prevention and Treatment of Osteoporosis*. *The Clinician’s Guide* provides recommendations to health care providers to help prevent, assess, diagnose and treat osteoporosis in men and postmenopausal women over 50 years of age.¹

Osteoporosis Overview

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mass and density, and is associated with bone weakness and an increased risk of fractures. It is estimated that 50% of all women and 20% of men over 50 years of age will develop a bone fracture due to osteoporosis. Fractures often occur in the proximal femur (hip), vertebrae (spine) and distal forearm (wrist). Fractures due to osteoporosis account for over 400,000 hospital admissions, 2.5 million medical office visits, and 180,000 nursing home admissions annually in the United States.¹

Estimates for 2005 were that 49% of women over 50 years of age had osteopenia of the femur and 10% had osteoporosis of the femur. Figures from the National Health and Nutrition Examination Survey (NHANES) 1988 – 1994 indicated that 7.3 million older men and women had osteoporosis of the femur and 26.3 million had osteopenia of the femur. In contrast, the estimates from the NHANES 2005-
2006 were that only 5.3 million older men and women had osteoporosis of the femur but 34.5 million had osteopenia of the femur. Thus although the incidence of osteopenia appears to be increasing there is a decline in the number of patients developing osteoporosis. Several explanations for this divergence have been suggested, such as that the increased use of medications such as bisphosphonates has reduced the prevalence of osteoporosis.²

**Bone Remodeling**

Bone remodeling is a continuous, lifelong process of bone resorption and bone formation to maintain normal bone mass. Remodeling begins when an injury or mechanical stress occurs in the bones. Osteocytes stimulate the release of growth hormone which then stimulates the production of osteoclasts. The osteoclasts will dissolve the surface of the bone matrix and create pits in the bone surface. This process is called resorption. The released growth hormone also stimulates bone formation by the release of osteoblasts, which fill the newly formed pits with new bone matrix. Calcium and phosphorus are incorporated into the matrix in a process known as mineralization. The lifespan of the osteoblasts is approximately three months, at which time most of the osteoblasts will mature into osteocytes that will reside in the bone matrix. These osteocytes are then ready to provide the signal to start the resorption/formation cycle. The osteocytes, osteoblasts and osteoclasts are also regulated by vitamin D, parathyroid hormone, calcitonin, testosterone, and estrogen.³

The rate of bone resorption and bone formation slows with age. In infants, the rate of remodeling is 100% of the bone annually, but by adulthood, the rate is 10% annually. In adults, bone formation does not completely restore 100% of the bone resorbed, resulting in a net loss of bone mass. This is a normal process in humans and explains the gradual loss of bone during aging. The imbalance in the regulation of bone remodeling, resorption, and formation results in bone diseases such as osteoporosis.⁴

**Risk Factors for Osteoporosis**

The range of risk factors for developing osteoporosis is varied. Lifestyle factors, genetic factors, hypogonadal states, endocrine disorders, gastrointestinal disorders, medications, gender and miscellaneous conditions and diseases all may
contribute to an increased risk of developing osteoporosis.¹ The following table summarizes common osteoporosis risk factors.

### Risk Factors for Developing Osteoporosis

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th>Genetic Factors</th>
<th>Hypogonadal States</th>
<th>Endocrine Disorders</th>
<th>Gastrointestinal disorders</th>
<th>Medications</th>
<th>Miscellaneous Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low calcium intake</td>
<td>Cystic fibrosis</td>
<td>Premature ovarian failure</td>
<td>Adrenal insufficiency</td>
<td>Celiac disease</td>
<td>Anticoagulants</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Smoking (active or passive)</td>
<td>Porphyria</td>
<td>Due to anorexia nervosa and bulimia</td>
<td>Diabetes Mellitus</td>
<td>Primary biliary cirrhosis</td>
<td>Anticonvulsants</td>
<td>Depression</td>
</tr>
<tr>
<td>More than 3 alcoholic drinks daily</td>
<td>Idiopathic hypercalciuria</td>
<td>Androgen insensitivity</td>
<td>Thyrotoxicosis</td>
<td>Gastric bypass</td>
<td>Glucocorticoids (≥5 mg/day of prednisone or equivalents for ≥ 3 months)</td>
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<tr>
<td>Thinness</td>
<td></td>
<td></td>
<td></td>
<td>Pancreatic disease</td>
<td></td>
<td>Renal disease</td>
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<tr>
<td>Sedentary lifestyle</td>
<td></td>
<td></td>
<td></td>
<td>Inflammatory bowel disease</td>
<td></td>
<td>Prior fracture as an adult</td>
</tr>
<tr>
<td>Low Vitamin D intake</td>
<td></td>
<td></td>
<td></td>
<td>GI surgery</td>
<td></td>
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<tr>
<td>Thinnness</td>
<td></td>
<td></td>
<td></td>
<td>Malabsorption</td>
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</tbody>
</table>

¹ Ref: 1,2,3

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Risk Assessment and Diagnosis of Osteoporosis

The recommendations put forth by the NOF include a comprehensive approach to the diagnosis and management of osteoporosis. Screening for osteoporosis includes a physical examination, a detailed history, a bone mineral density (BMD) assessment, and use of the WHO 10-year Estimated Fracture Probability calculation to determine the patient’s fracture risk.¹

The NOF guidelines recommend that the following populations be screened for osteoporosis:

- All women age 65 years and older
- All postmenopausal women under age 65 who have one or more additional risk factors for osteoporosis (in addition to being postmenopausal and female)
- Postmenopausal women who sustain a fracture
- Women who are considering therapy for osteoporosis if bone density testing would facilitate the decision
- Women who have been on hormone therapy for prolonged periods

Screening for men is not currently recommended in the NOF guidelines.

Several imaging tests are available. The dual-energy x-ray absorptiometry (DEXA) scan is the most commonly used imaging test for osteoporosis screening. It is considered accurate and sensitive; a DEXA scan can detect small changes in bone mineral density. The DEXA scan is non-invasive, uses minimal radiation, and is convenient and economically feasible.

The results of the DEXA scan can be reported as a T-score or a Z-score. The T-score is a comparison of the measured bone density to the average for the same gender at about 30 years of age. Bone mineral density peaks at about age 30 in women and men. The Z-score is used to compare the measured result to other patients of the same age, weight, ethnicity and gender. This test result may be used to determine unusual factors contributing to the patient’s bone loss such as thyroid abnormalities, malnutrition, adverse drug reactions and smoking.
A patient’s bone density is most commonly evaluated using the T-score. A T-score of greater than -1 is considered normal. A T-score of -1 to -2.5 is considered osteopenia, which is a moderate decrease in bone mineral density and is associated with an increased risk of developing osteoporosis. A T-score of less than -2.5 is diagnostic of osteoporosis.¹

### T-Score Results

<table>
<thead>
<tr>
<th>T-SCORE</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; -1</td>
<td>NORMAL</td>
</tr>
<tr>
<td>-1 TO -2.5</td>
<td>OSTEOPENIA</td>
</tr>
<tr>
<td>&lt; -2.5</td>
<td>OSTEOPOROSIS</td>
</tr>
</tbody>
</table>

### Treatment

According to the *Clinician’s Guide*, healthcare providers should consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) AND a 10-year probability of a hip fracture ≥ 3% OR a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinician’s judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Potential risks and benefits regarding osteoporosis treatments should be considered for each individual patient.¹
History of Bisphosphonates

Bisphosphonates were originally used as corrosion inhibitors in the textile, fertilizer and oil industries. Etidronate was first synthesized in 1898 and was the first bisphosphonate used to treat a human disease. The development and use of bisphosphonates to treat various bone, tooth and calcium metabolism diseases has become much more prevalent in the past 40 years. Although the focus of this monograph is on bisphosphonates used for osteoporosis, a brief summary of bisphosphonates used for other indications is provided in the Bisphosphonate Indications and Dosages section for reference.

Mechanism of Action

Bisphosphonates reduce bone turnover by inhibiting bone resorption. Bone mass and mineralization increase, and the resulting rise in bone strength reduces fracture risk. Bisphosphonates inhibit osteoclastic bone resorption by attaching to hydroxyapatite sites on the bone, especially on areas undergoing active resorption. As the osteoclast begins to resorb the bone matrix impregnated with the bisphosphonate, the released bisphosphonate impairs the ability of osteoclast to form a ruffled border necessary to adhere to the bone surface. Bisphosphonates also reduce osteoclast activity by promoting osteoclast apoptosis (cell death), and by decreasing osteoclast progenitor development and recruitment. There is evidence that bisphosphonates may also prevent osteocyte and osteoblast apoptosis.

Efficacy

The Fracture Intervention Trial (FIT), an early randomized controlled study which included 6,459 participants, looked at the incidence of bone fracture and changes in the BMD in patients taking alendronate versus placebo. The BMD increased 7-9% at the spine and increased 5-8% at the hip when compared to placebo. By the fourth year, new vertebral fractures decreased by 50% and hip fractures...
decreased by 56% for women who had osteoporosis but no prior vertebral fractures.  

In 2001, McClung et al published the results of the “Effect of Risedronate on the Risk of Hip Fracture in Elderly Women” in The New England Journal of Medicine. Over 5000 elderly women were treated in a double-blind study to determine the effectiveness of risedronate in the treatment and prevention of osteoporosis. The researchers concluded that risedronate prevented hip fractures in women who already had osteoporosis based upon a low bone mineral density at the femoral neck, but not in women who did not have osteoporosis, though they may have been at risk.

A meta-analysis published in 2005 reviewed the results of 12 studies that included 18,667 patients at risk for osteoporotic hip fracture, the most serious consequence of osteoporosis. The medications used in the studies included alendronate, risedronate, etidronate, and clodronate. The researchers concluded that overall the use of bisphosphonates reduced the incidence of hip fracture by 42%. In patients with a low BMD, at high risk of developing a osteoporotic fracture, or having documented osteoporosis, the risk reduction was determined to be 58.

Bisphosphonate Indications and Dosages

Bisphosphonates as a group affect bone formation. Within the group, each drug has a different indication profile. The optimal duration of use for osteoporosis has not been determined. All patients on bisphosphonate therapy require periodic re-evaluation for continual therapy.

Currently the bisphosphonates available include Fosamax® (alendronate), Actonel (risedronate), Boniva® (ibandronate), Reclast® (zoledronate) Zometa® (zoledronate), Didronel® (etidronate), and Aredia® (pamidronate). Alendronate, risedronate, ibandronate, and zoledronate (Reclast®) are indicated for the treatment of osteoporosis.

The other bisphosphonates, etidronate, pamidronate, and zoledronate (Zometa®), are indicated for various disease states. Etidronate is indicated for the treatment of symptomatic Paget’s disease of the bone, prevention and treatment
of heterotopic ossification following total hip replacement, and prevention and
treatment of heterotopic ossification due to spinal cord injury. Pamidronate is
indicated for Paget’s disease and for hypercalcemia of malignancy. In addition,
pamidronate is indicated for osteolytic bone metastases of breast cancer and
osteolytic lesions of multiple myeloma. Zoledronate (Zometa®) is indicated for
hypercalcemia of malignancy, for use in patients with multiple myeloma, and for
patients with bone metastases from solid tumors. In patients with prostate
cancer, the cancer should have progressed after at least one hormonal therapy.¹⁵-
¹⁷

Fosamax® (alendronate), available in tablets and an oral solution, has been shown
to reduce fractures of the hip, forearm and spine; alendronate has also been
shown to increase the BMD at the lumbar spine, femoral neck, and trochanter.
Hypocalcemia must be corrected prior to treatment with alendronate. Patients
with osteoporosis or Paget’s disease of the bone should receive calcium and
vitamin D if the dietary intake is insufficient. The alendronate dose is not modified
due to renal function if the creatinine clearance is greater than 35 ml/min.
Alendronate is not recommended for patients with severe renal insufficiency (CrCl
≤ 35 ml/min) due to lack of experience in this patient population.

Alendronate is indicated for:

- Treatment of osteoporosis in post-menopausal women
  - 10 mg daily or 70 mg weekly
- Prevention of osteoporosis in post-menopausal women
  - 5 mg daily or 35 mg weekly
- Treatment of osteoporosis in men
  - 10 mg daily or 70 mg weekly
- Treatment of osteoporosis in corticosteroid-induced osteoporosis
  - The recommended dosage is 5 mg daily during corticosteroid
    therapy. For postmenopausal women not taking estrogen, the
    recommended dosage is 10 mg daily.
- Paget’s disease of the bone
  - 40 mg daily for 6 months¹²
Fosamax Plus D® is an oral formulation of alendronate 70 mg with cholecalciferol (vitamin D3) either 2800 or 5600 IU. These dosages are taken once weekly.

Actonel® (risedronate) has been shown to decrease the risk of vertebral fractures and nonvertebral fractures, and to increase the BMD at the spine, hip, and wrist. The dosage is not adjusted in patients with mild to moderate renal impairment (CrCl ≥ 30 ml/min). Risedronate should not be administered to patients with poor renal function (CrCl < 30ml/min).

Risedronate is indicated for:

- Treatment and prevention of postmenopausal osteoporosis
  - The dosages are: 5 mg daily, 35 mg weekly, 75 mg two consecutive days each month, or 150 mg monthly
- Treatment to increase bone mass in men with osteoporosis
  - The dose is 35 mg weekly
- Treatment and prevention of glucocorticoid-induced osteoporosis
  - The dose is 5 mg daily
- Treatment of Paget’s disease
  - The dose is 30 mg daily for 2 months

Boniva® (ibandronate) increases the BMD at the lumbar spine and hip, and decreases the incidence of vertebral fractures. Ibandronate does not reduce the incidence of nonvertebral fractures (pelvis, femur, wrist, forearm, rib and hip). The dosage is not adjusted in patients with mild to moderate renal impairment (CrCl ≥ 30 ml/min). Ibandronate should not be administered to patients with poor renal function (CrCl < 30ml/min). The manufacturer recommends that patients receiving the intravenous formulation also receive supplemental calcium and vitamin D.

Ibandronate is indicated for:
• Treatment and prevention of osteoporosis in postmenopausal women
  Ibandronate is dosed at either 2.5 mg orally daily, 150 mg orally monthly or 3 mg IV every 3 months\textsuperscript{13,18}

Reclast\textsuperscript{®} (zoledronate), an intravenous infusion, is reserved for patients who cannot tolerate an oral bisphosphonate. The dosage is not adjusted in patients with mild to moderate renal impairment (CrCl $\geq$ 35 ml/min). Zoledronate should not be administered to patients with poor renal function (CrCl $<$ 35ml/min) and to those patients exhibiting evidence of acute renal impairment. The risk of acute renal failure may increase in underlying renal disease and dehydration secondary to fever, sepsis, advanced age, and more. It is important that patients are appropriately hydrated prior to zoledronate administration. Zoledronate is pregnancy category D and should not be used during pregnancy. The patient may take acetaminophen following the infusions to reduce the incidence of APR symptoms. The indications are:

• Treatment of osteoporosis in postmenopausal women and in men
  5mg intravenously once yearly over no less than 15 minutes

• Prevention of osteoporosis in postmenopausal women
  5 mg intravenously once every 2 years

• Treatment and prevention of glucocorticoid-induced osteoporosis

• Treatment of Paget’s Disease of bone in men and women
  5mg intravenously

To reduce the risk of hypocalcemia, all patients being treated for Paget’s Disease of Bone should receive 1500 mg elemental calcium in 2 – 3 divided doses and 800 IU vitamin D daily, especially in the 2 weeks following zoledronate administration.\textsuperscript{19}
Comparisons of the Various Bisphosphonates used for Osteoporosis Treatment and Prevention

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Indications for Use</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax®, Fosamax Plus D®)</td>
<td>• Treatment of osteoporosis in post-menopausal women</td>
<td>• Increases the BMD of the spine, hip, wrist and total body</td>
</tr>
<tr>
<td></td>
<td>• Prevention of osteoporosis in post-menopausal women</td>
<td>• Decreases the risk of vertebral (spine) fractures</td>
</tr>
<tr>
<td></td>
<td>• Treatment of osteoporosis in men</td>
<td>• Decreases risk of wrist, hip and all nonvertebral fractures</td>
</tr>
<tr>
<td></td>
<td>• Treatment of osteoporosis in corticosteroid-induced osteoporosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Paget’s Disease of the bone</td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>• Treatment and prevention of osteoporosis in postmenopausal women</td>
<td>• Increases BMD at the spine, hip and wrist</td>
</tr>
<tr>
<td></td>
<td>• Treatment to increase</td>
<td>• Increases BMD at lumbar spine, femoral neck, femoral trochanter and</td>
</tr>
<tr>
<td>Bone Mass in Men</td>
<td>Midshaft Radius</td>
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<td>------------------</td>
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<tr>
<td>• Treatment and prevention of glucocorticoid-induced osteoporosis</td>
<td>• Decreases incidence of new and worsening vertebral fractures</td>
<td></td>
</tr>
<tr>
<td>• Treatment of Paget’s Disease of the bone</td>
<td>• Decreases incidence of new and worsening nonvertebral osteoporosis-related fractures</td>
<td></td>
</tr>
</tbody>
</table>

**Ibandronate (Boniva®, Boniva Injection®)**

- Treatment and prevention of osteoporosis in postmenopausal women
- Decreases risk of new vertebral fractures
- Increases the BMD at the lumbar spine and hip

**Zoledronate (Reclast®)**

- Treatment and prevention of postmenopausal osteoporosis
- Increases BMD at lumbar spine, total hip and femoral neck
- Decreases incidence of new vertebral fractures
- Decreases incidence of hip fractures
- Decreases incidence of nonvertebral fractures
- Decreases the rate at which height is lost
Administration

Oral bisphosphonates should be taken at least 60 minutes before the first food or drink of the day, except for six to eight ounces of water, and before taking any oral medication including calcium, antacids, or vitamins. Patients should remain upright and not lie down for at least 30 minutes after taking their dose. These directions will help prevent the esophagitis and upper gastrointestinal inflammation and pain that can result from bisphosphonate use.12-14,16

It is recommended that the patient’s calcium intake is assessed before and during bisphosphonate therapy. Bisphosphonates are most effective when the patient is not hypocalcemic. Dietary calcium and vitamin D should be adequate during bisphosphonate therapy. The co-administration of calcium and a bisphosphonate will decrease the bioavailability of the bisphosphonate. It is recommended that calcium be administered 2 hours after the bisphosphonate dose.9-11

Vitamin D is necessary for bone development by increasing the absorption of calcium. Decreased calcium absorption, bone loss, and an increased risk of fractures are associated with vitamin D insufficiency.21 Recently, Shieh A et al (2011) announced results of a study looking for a correlation between vitamin D levels and bisphosphonate response. The researchers found that women with vitamin D (24(OH)D) levels above 33 ng/ml were seven times more likely to respond to bisphosphonate therapy than women with vitamin D levels less than 33 ng/ml.22

The length of bisphosphonate therapy for optimal response is uncertain. Clinical trial results determining the length of treatment guidelines in prevention of fractures are still inconclusive. Patients receiving bisphosphonate therapy should be re-evaluated periodically to assess the need for continual treatment.12-14,17,19

Pharmacokinetics
Bisphosphonates are poorly absorbed from the gastrointestinal tract when taken orally. Normally less than 1% of an oral dose is absorbed, of which 50% is taken up by the bone, and the remaining amount is excreted unchanged in the urine.\textsuperscript{23} The half-life of bisphosphonates has been estimated to be 10 years.\textsuperscript{20} Recently, Brown et al looked at the prolonged effects of a single dose of zoledronate in patients with osteopenia or a low BMD. The researchers found that at 36 months after the single treatment, 90% of the treated study patients achieved an increase of 4.3% of the BMD at the hip, and 84% of the treated study patients achieved an increase of 5.3% of the BMD in the lumbar spine. The authors concluded that the infrequent administration of a bisphosphonate may provide a sustained increase in BMD while offering increased convenience, reduced toxicity, and reduced cost to the patient.\textsuperscript{24}

**Contraindications**

The oral bisphosphonates are contraindicated in patients who show abnormalities of the esophagus with delayed esophageal emptying, are unable to sit or stand upright for at least 30 minutes after taking the dose, are not cognitively able to follow the directions for dosing, and in patients with untreated hypocalcemia. Alendronate, risedronate, and ibandronate are pregnancy category C and should not be taken during pregnancy.\textsuperscript{12-14} Zoledronate is pregnancy category D and should not be administered during pregnancy; it is contraindicated in uncorrected hypocalcemia and renal failure.\textsuperscript{19}

**Adverse Effects**

The side effect profile for bisphosphonates includes fatigue, constipation, nausea, vomiting, anemia, gastritis, myalgia, and arthralgia and bone pain. The incidence of gastritis is increased if the patient chews the medication or lies down after a dose. It is important that the patient follows the directions for administration.\textsuperscript{12-14}

Other more serious side effects have been reported. Acute phase reactivation (APR) is a flu-like syndrome seen in patients shortly after receiving intravenous
infusions of pamidronate and zoledronate. The patients may experience fever, chills, flushing, bone pain and/or arthralgias and myalgias. The bisphosphonate should be discontinued if severe symptoms occur.

There have been reports regarding the association of atypical femur fractures in patients taking bisphosphonates. A study published in 2011 which looked at 12,777 women aged 55 years and older showed an increased rate of atypical fractures of the femoral shaft. Most of the atypical fractures occurred within the last year of bisphosphonate use. It has been suggested that the use of bisphosphonates allow the accumulation of microcracks leading to stress fractures or fatigue fractures. The study results also showed a 70% risk reduction in atypical fractures yearly following the discontinuation of bisphosphonate therapy. The researchers concluded that the absolute risk to be 5 cases per 10,000 patient-years and that the benefits of bisphosphonate therapy outweigh the risk of atypical fractures.25

Bisphosphonate associated osteonecrosis of the jaw (BAONJ) was first described in medical literature in 2003. Osteonecrosis of the jaw occurs when the jaw bone is exposed and begins to starve from a lack of blood. The bone weakens and dies which may or may not cause pain. The cases reported have been principally in patients with cancer and who have received bisphosphonate treatment; osteonecrosis was most commonly observed in the patients who had received IV bisphosphonate therapy. Through a comprehensive literature review, Khan et al (2009) reported the rate of bisphosphonate associated BAONJ may be 1-12% after 36 months of bisphosphonate therapy for oncology patients receiving high doses of bisphosphonates. In patients being treated for osteoporosis, the bisphosphonate associated BAONJ is <1/100,000 person-years of exposure.26 The incidence of BAONJ was associated with a greater frequency in patients with certain cancers such as breast cancer and multiple myeloma.17 Although the dosage, route of administration, and duration of bisphosphonate therapy seem to relate to the occurrence of BAONJ, immune and infectious factors may also be involved.

For most patients the benefits of bisphosphonate therapy outweigh the risk of BAONJ.27 Patients should be counseled to have a prophylactic dental examination
before initiating intravenous bisphosphonate therapy and to avoid invasive dental procedures during intravenous bisphosphonate therapy.\textsuperscript{15,17,19}

**Conclusion**

Bisphosphonate therapy may provide significant benefits. Today we are fortunate to have a variety of antiresorptive agents that reduce the incidence of vertebral and nonvertebral fractures, including those of the spine, hip, and wrist. The end result is a reduction in morbidity and mortality, and an increase in patients’ quality of life. It is important to continue to help patients and caregivers with the questions and concerns they may have. Pharmacists can help ensure therapy success by reminding patients to take the bisphosphonates at the proper interval, early in the day prior to eating and drinking, and to report any side effects to their health care provider.
References


