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Clinical Management of Osteoporosis Fractures with Bisphosphonate Therapy

Susana B. Njuakom

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Susana B. Njuakom

University of North Dakota

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Abstract

Fractures are the clinical sequelae of osteoporosis and they carry significant morbidity and mortality risks. Bisphosphonates (BP) have transformed therapy for management of osteoporosis and are widely used as first line with proven effectiveness from randomized clinical trials in the prevention of vertebral and non- vertebral fractures. However, long term bisphosphonate therapy has been associated with some pathologic conditions such as osteonecrosis of the jaw, atypical femur fractures, esophageal cancer and atrial fibrillation, which has raised serious concerns about safety of bisphosphonates.

Objective: To examine the efficacy of bisphosphonate therapy in the prevention and treatment of osteoporosis and osteoporosis related fractures as well as highlight some areas of concern associated with bisphosphonate use.

Key Words: Bisphophonates, Osteoporosis management, bisphosphonates and clinical practice

was used on PubMed to identify relevant publications for inclusion. Search was limited to articles within the last 10 years. Additional literature was obtained from reference lists of some of the publications, this included older research articles on bisphosphonates.

Background

Osteoporosis is a metabolic bone disease characterized by a decrease or loss of bone mineral density (BMD) resulting in increased porosity of the skeleton and increased susceptibility to fractures (Porth & Matfin, 2009). The World Health Organization defines osteoporosis as bone mineral density (BMD) < -2.5 SD or more from the young adult mean. Fractures and their complications are the most common clinical sequelae of osteoporosis. Most common fractures sites are; the hip, spine, and wrist. The American Academy of Orthopedic Surgeons (AAOS) estimates that osteoporosis currently affects more than 200 million people worldwide and with more than 10 million being from the United States alone and another 18 million at risk for developing the disease (2014).

Data from the National osteoporosis foundation (NOF) estimates that one of every two Caucasian females in the United States (US), will experience an osteoporosis-related fracture at some point in her lifetime, as well as one in five men (2010). Fractures can have major life changing physiological, psychological and economic consequences on individuals such as; disability, chronic pain, life style and cosmetic changes, fear, anger anxiety, depression, strained relationships due to the high morbidity and dependency associated with fractures and death (NOF, 2010). Hip fractures alone result in 10 to 20 percent increase in mortality within one year and are associated with a 2.5 fold increase in the risk for future fractures with only 40% of hip fracture patients regaining their pre-fracture level of independence (Eisenberg, Placzek, Gu, Krishna & Yulsi, 2015, p. 56,). Vertebral fractures are also associated with increased morbidity and mortality with some of the complications being; back pain, kyphosis and loss of height (NOF, 2010). Postural changes associated with kyphosis may limit activity, including bending and reaching. Multiple thoracic fractures may result in restrictive lung disease, and lumbar

fractures may alter abdominal anatomy, leading to constipation, abdominal pain, distention, reduced appetite and premature satiety. Wrist fractures are less globally disabling but can interfere with specific activities of daily living as much as hip or vertebral fractures (NOF, 2010).

Osteoporosis-related fractures also carry a heavy economic burden in the United States. Data from the NOF indicates that fractures account for more than 432,000 hospital admissions annually, 2.5 million medical office visits and 180,000 nursing home admissions annually. The acute and long-term medical care expenses associated with osteoporosis related fractures in the US are estimated to rise from $17 billion in 2005 to $474 billion in two decades due to the aging population (AAOS, 2014). Prevention by identifying risk factor and providing treatment and education is the key to decreasing the high mortality and morbidity associated with osteoporosis.

An estimated 30% of women and 19% of men aged 50 and older in the USA are at increased risk for osteoporotic fracture and are eligible for pharmacologic treatment to prevent life threatening fractures (Modi, Shiva & Ghandi, 2014). FDA approved pharmacologic treatment options for prevention and management of osteoporosis and related fractures are bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid), calcitonin, estrogens and/or hormone therapy, parathyroid hormone (teriparatide) and estrogen agonist/antagonist (raloxifene). Of all these treatment options, bisphosphonates (BP) are the recommended first line therapy for osteoporosis prevention and treatment.

Case Report

The Objective Structured Clinical Examination (OSCE) scenario involved a 68 year old Caucasian female with a 30 pack year smoking history presents for follow up after a hip replacement surgery for a complete intertrochanteric fracture following a fall at her home six months ago. Her past medical history is significant for hypertension and stage II breast cancer. She lives a sedentary life, does not like yogurt or milk and does not take Calcium or vitamin supplements. No significant family history of metabolic disease or thyroid problems. She rates her pain at 3/10 and takes OTC Tylenol for pain management. Her vitals are stable, she has no known allergies

She was negative for fever, shortness of breath, palpitations, chest pain, dizziness or light-headedness during the follow up appointment. She rated her pain 4/10 which was well relieved and controlled by Tylenol. She reported a sedentary lifestyle; a 30 year packs history, no calcium or vitamin D, milk or yoghurt intake.

Past Medical and Surgical History

1. Hypertension
2. Breast Cancer Stage II
3. Total Right Hip Replacement

Allergies: None

Medications:

Lisinopril (Zestril) 10 mg once daily,

Arimidex 1 mg tablet PO once daily

Tylenol 500mg 2 tablets PO prn

Social History: 50 pack years, widowed, no exercise. Works at local sugar company, mother to 3 grown children and has 5 grand-children.

Review of Systems:

Constitutional: negative for unintentional weight loss, or fever.

Respiratory: Denied shortness of breath, or wheezing.

Cardiovascular: Denied chest pain/discomfort or palpitations.

Musculoskeletal: Patient denied joint pain and arthritis, or muscle pain and weakness. She reported residual pain as the right hip, rated pain 4/10. Able to ambulate with use of a cane. Pain well controlled by Tylenol.

Neurologic: denied paresthesia, seizures, loss of sensation, numbness or tingling.

Physical Exam:

Vital signs: T 98.1HR 82, BP 144/852, RR 14, Ht: 60, Wt. 200, BMI 34,

General: 68 year old Caucasian female in no acute distress. Good hygiene, cooperative, and pleasant demeanor. She appeared stated age.

HEENT: Head - Normocephalic, atraumatic.

Cardio: Heart rate and rhythm regular without murmurs, gallops, clicks,

RESP: Lungs sounds clear. No wheezing or rales.

Musculoskeletal: Surgical scar visible to right hip on the lateral side. It is healed and approximated and without bruising, tenderness, swelling, erythema or warmth. Active and passive range of motion to bilateral lower extremities was within limits. No tenderness on internal or external rotation.

Neurologic: Deep tendon reflexes intact to bilateral lower extremities.

Diagnostics:

1. DEXA Scan: T score of the Lumbar spine is -4.1 which is consistent with the WHO classification for established osteoporosis. T score of the femoral neck is -2.1 which consistent with the WHO classification for osteopenia with high risk for fracture.

2. CBC, CMP, Creatinine Clearance- No significant finding

Differential diagnosis: Osteoporosis, osteomalacia, osteonecrosis, and metastatic bone disease which is less likely due to normal CBC and CMP.

Plan:

Osteoporosis:

- Start Reclast at 5 mg IV infusion yearly
- Supplement Calcium with 1500 Once daily
- Supplement Vitamin D intake with 1000 mg daily.
- Patient education on Reclast including the therapeutic and adverse effects of the medication was given. She was also encouraged to engage in physical activity for at least

30 minutes, 5 times/ week and to include muscle strengthening exercises such as swimming (Dunphy, Brown, Porter, & Thomas (2011).

- Refer to PT

Review of Literature

The efficacy of Alendronate, a nitrogen containing bisphosphonate approved for the prophylaxis and treatment of fractures was illustrated during the Fracture Intervention Trial (FIT); a randomized, blinded, placebo- controlled trial that was done in the 90s. According to Boonen, (2007), the FIT trial, included 2027 women aged between 55 and 81 with an existing vertebral fracture and 4432 females with established osteoporosis defined by a T- score < -2.5 at the femoral neck with no history of a vertebral fracture. The women were randomized to Alendronate 5 mg for 2 years and 10 mg the third year or to a placebo group. The study found significant reductions in clinical vertebral fracture risks in the Alendronate group compared to the placebo group within a year. There was a 59% decrease in the risk for vertebral fractures in the study group within a year (Boonen, 2015).

A randomized, double blind, placebo-controlled clinical trial called the Vertebral Efficacy with Risedronate Trial (VERT) was conducted at over eighty centers in Europe, Australia and North America to determine the efficacy and safety of Risedronate in the prevention of vertebral fractures in postmenopausal women under 85 years of age with established osteoporosis and a history of 1 or more vertebral fractures. The trial included 2458 participants who were either randomized to a treatment group and given 2.5 or 5 mg of Risedronate daily, or a placebo group. All subjects received calcium, 1000 mg/d and vitamin D (cholecalciferol, up to 500 IU/d) if baseline levels of 25-hydroxyvitamin D were low. After

reviewing data from other trials, it was determined that 2.5 mg of Residronate was less effective than 5 mg in the management of vertebral fractures. The 2.5 mg group was discontinued one year into the study. However, the findings for the 5 mg group was staggering. Overall, Risedronate administered at 5 mg reduced the risk of new vertebral fractures by 49% over a period of 3 years compared to the control group ($p<0.001$). A significant reduction of 61% was also seen within the first year of starting the medication ($p = 0.001$). The fracture reduction with Risedronate 2.5 mg was similar to that in the 5 mg group over 2 years. The risk of non-vertebral fractures was reduced by 33% compared with control over 3 years ($p = 0.06$) (Reginster, Minne, Sorensen, Hooper, Roux, Brandi, Lund, Ethgen, Pack, Roumagnac, Eastell, 2000).

Bisphosphonates are also effective at treating non vertebral fractures. According to Boonen (2007), the efficacy of Alendronate and Residronate in decreasing the risk of non-vertebral fractures was established by afore mentioned FIT trial. Data from a pooled group of women who had documented osteoporosis at baseline indicated a decreased fracture risk for non-vertebral fractures by up to 27% in post-menopausal women with osteoporosis following treatment with bisphosphonates. A post hoc analysis of the Hip Intervention Program (HIP) study which was a randomized controlled trial comparing Risedronate with placebo for reducing the risk of hip fracture in elderly women aged 70-100 year old over a 3 year period showed a statistically significant decrease in the incidents of hip fractures among participants in the treatment group compared to the placebo. There were 1656 Study participants all with established osteoporosis as defined by a femoral neck T score < -2.5 and a history of at least 1 baseline vertebral fracture. Hip fractures occurred in 7.4 % of participants in the placebo group compared to 3.8% in the Risedronate (Masud, McClung & Geusens, 2009).

In a double-blind, placebo-controlled trial by Black, Delmas, Eastell, Reid, Boonen, Cauley, Cosman & Man, (2007), 7765 women with post-menopausal osteoporosis and a mean age of 73 years were followed for a period of 3 years. Half of the patients were randomly assigned to the treatment group and received a single 5 mg infusion of zoledronic acid over 15 minute at baseline, 1 year, and 2 years. The other half were assigned to a placebo group with primary end points being to study new vertebral fractures in patients not taking other osteoporosis medications and hip fracture in all patients. There was a 70% decrease in the risk for morphometric vertebral fractures and a 41% decrease in the risk for hip fractures compared to placebo over 3 years. The risk for non-vertebral fractures was reduced by 25%, clinical fractures reduced by 33% and clinical vertebral fractured declined by 77% in the treatment group compared to placebo group. In another study, annual treatment with Zoledronic acid over a two years period led to a 6% increase in lumbar spine bone mineral density (BMD) compared with baseline in men with osteoporosis (Maricic, 2010).

Based on findings from the afore mentioned studies and numerous other studies, it is safe to state that, bisphosphonates are reliable and efficacious in the treatment of osteoporosis and osteoporosis related fractures. They can also be used prophylactically for fracture prevention in patients with low BMD. However, they are not without side effects. Some of the adverse effects associated with bisphosphonate therapy are; gastrointestinal irritability, flu-like symptoms, atypical femoral fractures, atrial fibrillation, osteonecrosis of the jaw, ocular inflammation and esophageal cancer.

Gastrointestinal (GI) irritation is one of the most common side effects of oral bisphosphonate therapy and the most common reason for non-adherence to treatment (Xu, Gou, Wang, Guo, Lu, Lu & Peng, 2013). Up to 20% of people on oral bisphosphonates discontinue

treatment due to upper GI discomfort (Reid, 2011). According to Abrahamsen, (2010), endoscopic studies have revealed gastric erosion in patients the first week after initiating treatment with Alendronate and Risedronate. A blinded endoscopic study of 500 otherwise healthy postmenopausal females found a three-fold increase in the incidents of gastric ulcers in patients on Alendronate compared to Risedronate (Abrahamsen, 2010). It is best to avoid oral agents in patients with active upper gastrointestinal problems or experience delayed esophageal emptying. Patient teaching regarding dosing regimens should be provided to minimize intolerance and ensure peak absorption. Pills should be taken on an empty stomach (fasting) with water and patient should remain in an upright position after dosing. Flu-like symptoms have also been linked to Intravenous bisphosphonates. These symptoms occur in about 30% of cases and often occurs after the initial dose. The severity of the symptoms decrease after the second dose (Reid, 2011). Although this is non-life threatening, it may progress to musculoskeletal distress in some patients lasting up to two weeks. But this is quite rear.

In 2011, the Food and Drug Administration (FDA) issued a safety review of oral bisphosphonate and a potential increase in the risk of esophageal cancer. There were 23 cases of patients in the United States diagnosed with esophageal cancer after starting oral bisphosphonates. In twenty one of the twenty three cases, alendronate was listed as the suspect drug and in the two other cases; it was listed as a concomitant drug. 31 cases were also reported in Europe and Japan with oral bisphosphonates also suspected as the origin of the cancer. In a US study on Medicare beneficiaries who started oral bisphosphonates, esophageal cancer rate was reported to be 0.27 cases per 1000 people. A corresponding Danish study on patients receiving oral bisphosphonates reported esophageal cancer rates at 0.48 cases/ 1000 (Abrahamsen, 2010).

A study by Black et al, (2007) on the effects of annual infusions of zoledronic acid on fracture risk over a 3-year period had some compelling findings. Although they found Zoledronic acid to be effective at decreasing the risk for fractures, they also found it to increase the incidents of atrial fibrillation in the zoledronic acid group compared to the placebo group. There were 50 cases of atrial fibrillation in the treatment group compared to 20 in the placebo group. A meta-analysis of five randomized control trials and four observational studies (total of nine studies) which examined the risks for atrial fibrillation with the use of oral and intravenous bisphosphonates also found a positive correlation between bisphosphonates (oral and I.V.) and atrial fibrillation. There was 1.1% increased risk for atrial fibrillation in patients on IV agents and a 0.4 % risk in patients on oral agents (Sharma, Einstein, Vallakati, Arbad-Zadeh, Walker, Mukherjee, Homel, Borer, & Lichstein, 2014). Although the absolute risk is low, it is important for providers to watch for and educate patients about it, especially patients with pre- existing cardiac conditions.

Several reports have surfaced since early 2000 linking bisphosphonate use to the development of osteonecrosis of the jaw (ONJ). The task force of the American Society for Bone and Mineral Research defines ONJ as "the presence of exposed bone in the maxillofacial region that did not heal within eight weeks after identification by a healthcare provider" (Papapetrou , 2009). The incidence of ONJ is reported to increase over time with continuous exposure to bisphosphonate therapy from 1.5% among patients treated for four – twelve months to 7.7 % for those treated for 3-4 years. The risk for cancer patients treated with high doses of IV bisphosphonates is estimated at 1-10 per 100 patients depending on the length of treatment. For patients with osteoporosis or Paget's disease, the risk is estimated at between 1 in 10,000 and 1 in 100,000. Sixty percent of cases occurred after a dental procedure and the remaining forty

percent occurred spontaneously (Papapetrou, 2009). Identified risk factors include; periodontal disease, dental procedure involving bone surgery, trauma from poorly fitting dentures, underlying malignancy, corticosteroid use, chemotherapy and infection.

Several studies have also linked bisphosphonates to atypical fractures most of which comprise of low energy, subtrochanteric or proximal femoral shaft fractures. A 2005 study by Odvina, Zerwekh, Rao, Maalouf, Gottschalk & Pak reported nine patients on long term therapy with alendronate who sustained spontaneous low energy, non-spinal fractures. Of the 9 patients, 5 sustained femoral shaft fractures, with two sustaining them bilaterally. Bone biopsies showed excessive suppression of bone turnover which quite possibly led to bone fragility. Six of the patients also displayed either delayed or absent fracture healing for 3 months to 2 years during therapy. A retrospective analysis of more than fifteen thousand femoral fractures in the United States identified 142 radiographic confirmed cases of patients with atypical fractures. 128 of the 142 were on bisphosphonate therapy for an average of 5 years. The risk for atypical fractures for patients on bisphosphonates was estimated to increase from 1.78 atypical femoral fractures/ 100 thousand patients a year, to 113 atypical fractures/ 100 thousand per a year when treatment continues for 8-10 years (McClung, Harris, Miller, Bauer, Davison, Dian, Hanley & Lewiecki, 2013). The total incidence of fractures was 7.8 per 100 thousand a year for people aged 60 and older and 0.8 per 100 thousand for people aged 15-60 years (Papapetrou, 2009). The risks for atypical fractures diminish substantially when patients are taken off bisphosphonates.

A 2008 FDA review of clinical trials on the relationship between bisphosphonates and Atrial fibrillation revealed no clear relationship between the two whether severe or not. The FDA's Med watch recommended that healthcare professionals should continue with the same

prescription patterns and also encourage patients to continue on their treatment regimen. Regarding claims of a link between bisphosphonates and ONJ and atypical fractures,

Learning Points

Bisphosphonates are crucial in the treatment of patients with post-menopausal osteoporosis, male osteoporosis and secondary osteoporosis. In spite of some of the serious side effects listed above, the benefits outweigh the risk of taking it prophylactically or for actual treatment of osteoporosis.

The benefits of bisphosphonates go beyond reducing fracture risk. It significantly decreases morbidity, mortality and treatment cost. It also leads to increased survival and quality of life. McClung et. Al, (2013) estimate that bisphosphonates decrease mortality rate by up to 28% for patients with recent low trauma hip fractures when compared non users.

The risk of ONJ, atrial fibrillation and atypical subtronchanteric fractures when taking bisphosphonate is minimal compared to the anti-fracture benefits provided to at risk individuals (McClung, Harris, Miller, Bauer, Davison, Dian, Hanley & Lewiecki, 2013).

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