3-28-2019

Duration of Bisphosphonate Therapy for the Treatment of Osteoporosis

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DURATION OF BISPHOSPHONATE THERAPY FOR THE TREATMENT OF OSTEOPOROSIS.

NURS 997 Independent Study

Family Nurse Practitioner Program

University of North Dakota

Monica Schonteich, FNP Student

PERMISSION

Title: Duration of Bisphosphonate Therapy for the Treatment of Osteoporosis.

Department: Nursing

Degree: Master of Science

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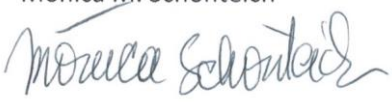
Signature: 

Date: 3/29/2019

Abstract

Bisphosphonates are considered first line therapy for the prevention and treatment of osteopenia and osteoporosis among post-menopausal women. They have proven efficacious in the reduction of fractures related to low bone mineral density. In the last few years, severe adverse effects have been linked to the long-term use of bisphosphonates, including osteonecrosis of the jaw and atypical femur fracture. In spite the fact that the aforementioned side effects are concerning for patients and providers, these complications are extremely rare compared to the prevalence of fractures among post-menopausal women. Currently, there are no definite guidelines for the duration of treatment with these medications.

This paper evaluates the treatment plan for a 72-year-old female with osteoporosis. While she is considered a high-risk patient due to a recent fracture and a T-score of -2.6, she is not on anti-osteoporosis medication. Through this report, selection of a bisphosphonate drug and duration of treatment for this particular patient will be addressed.

In order to better understand how to manage osteoporosis treatment with bisphosphonates, a review of the literature was conducted. MEDLINE, CINAHL, PubMed and Cochrane databases were searched. Articles from peer-reviewed journals, systematic reviews, retrospective studies and current guidelines from bone health organizations were reviewed. This research allows for a much clearer understanding of the association between bisphosphonates and severe adverse effects, and their role in the prevention and treatment of osteopenia and osteoporosis among post-menopausal female patients, as well as their role in the reduction of fractures.

Background

After the age of 40, an imbalance between bone breakdown and bone regeneration occurs due to changes in cell activity involved in bone tissue maintenance. In women, this imbalance accelerates after menopause due to the loss of estrogen and bones become weak, increasing their risk of fractures (American Academy of Orthopedic Surgeons, 2019). Estrogen-receptors activation in bone tissue sustain a synchronized process between osteoblasts, the cells that promote bone regeneration, and osteoclasts, the cells that break down bone, sustaining healthy bone tissue (Khalid & Krum, 2016). However, during menopause estrogen receptors are no longer activated resulting in an imbalance between building and destruction of bone. Osteoblasts slow down while osteoclasts continue to work at the same rate as they did in earlier years (Mayo Clinic, 2019) leading to the formation of weaker bones. Is in this scenario that osteopenia and osteoporosis develop. The standard method for measuring bone mineral density (BMD) is the axial dual-energy X-ray absorptiometry (DXA) (American Association of Clinical Endocrinologists & American College of Endocrinology, 2016). The result of this test is reported as a T-score and is interpreted according to the World Health Organization criteria for the diagnosis of osteoporosis. A T-score of -1.0 or above indicates a normal BMD, a T-score between -1.0 and -2.5 is considered low BMD or osteopenia, and a T-score of -2.5 or below confirms diagnosis of osteoporosis (National Osteoporosis Foundation, 2019).

The case study in this paper concerns a 72-year-old female who comes to the clinic for a 6-week follow up after being in the hospital for 3 days. She sustained a fall and broke her right hip. During her hospital stay she had an open reduction internal fixation (ORIF) surgery. This patient is a smoker and has been on oral steroid medications intermittently due to COPD. She is also on inhaled corticosteroids daily. Currently, she is neither on any anti-osteoporosis

medication nor on calcium-vitamin D supplements. She has never received treatment for osteoporosis in the past. This patient has a diagnosis of osteoporosis according to her most recent DXA scan, done 2 years ago, with a T-score of -2.6. According to most bone health organizations' recommendations, this patient should initiate pharmacologic treatment. This review focuses on the use of bisphosphonates in the management of osteoporosis.

Bisphosphonates (BP) are considered first line therapy for the prevention and treatment of bone density loss among post-menopausal women. They work by inhibiting osteoclasts activity allowing more time for bone matrix regeneration by osteoblasts (American Bone Health, 2019). The efficacy of BP in reducing fracture risk has been strongly proven in 3 main studies: The FIT-FLEX study, the HORIZON and its extension trial, and the VERT-MN study. These studies evaluated alendronate, zoledronate and ibandronate respectively. The authors concluded that full benefits of BP therapy can be achieved within a treatment period of 3 to 5 years, depending on the drug used. After this period, guidelines are not definite, leaving clinicians in a blurry path for treatment planning.

New discussions on BP therapy length have taken place due to concerns about severe adverse effects and based on the particular pharmacologic activity of these drugs. Research on the mechanism of action of BP has shown that after stopping the intake of these medications, their bone-protective function remains in the body. These drugs accumulate in bone tissue creating a reservoir of BP that maintains the inhibition of osteoclasts resorptive activity. In addition, investigations have shown that long-term use of BP has been associated with severe complications such as osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF) and esophageal cancer (Schneider, 2015). Although the risk of these adverse effects is low, in 2011 the FDA suggested a review of BP therapy with clarification on the duration of bisphosphonate

use. The panel of experts was unable to get to a conclusion (Diab & Watts, 2013), however, and instead they declared a limitation of bisphosphonate use - "The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy must be re-evaluated on a periodic basis" - FDA (Adler et al., 2016).

In order to properly delineate a plan for the management of osteoporosis for the patient in the case study, it was necessary to undertake a review of the literature to understand more clearly the prevalence of the severe side effects mentioned earlier after long-term intake of BP, and to evaluate the efficacy of bisphosphonates in the reduction of fractures. The purpose of this paper is to search for studies conducted to define the ideal duration of bisphosphonate therapy, and to review current practices and recommendations that can aid providers when deciding whether to star/restart, pause or stop bisphosphonate therapy.

Case Report

Allergies: none
Immunizations: Influenza 11/2018, Tdap 5/2015, Zoster live 5/2016, PCV13 1/2018
Chief Complaint: follow up after hospital discharge. Status post right ORIF surgery and to establish care.

HPI
Mary Jones is a 72-year-old female Caucasian patient, she is here for a follow up after being discharged from the hospital 6 weeks ago. She had a right hip surgery due to a "silly" fall she sustained when walking from her living room to the kitchen. She lost her balance trying to not to step on her little dog, she fell on her knee first and then she fell over her right side. She was surprised to find out that she broke her hip and not her knee.

Today she is doing good. She rates her pain at 3/10. Pain increases to 5/10 when doing her exercises but after taking Tylenol she is ok. She feels slightly fatigued but doing most of her shores by herself. She is using a walker to ambulate. Her children are helping her with groceries but other than that she is able to live independently in her house as she was before the fracture.

She would like also to establish care today. She tells me she has history of COPD, depression, anemia, hypertension, hypercholesterolemia and osteoporosis. She is a smoker. She smokes a pack per day, she has been doing it for more than 30 years.

Past Medical History:	**Past Surgical History:**	**Family History:**	**Social History**:
COPD Anemia Hypertension Hypercholesterolemia Depression	Right ORIF	Hypertension - Father Heart disease, Osteoporosis - Mother No siblings	She is a widow, living independently at home. She has 2 children who live in town and they have been helping her with shores because of the surgery. Occupational history: retired teacher. Smoke/alcohol/drugs: Smoker, 1 pack per day for more than 30 years/never used alcohol/never used drugs.

Home Medications:
Fluticasone propionate and salmeterol 250/50 1 puff BID
Prednisone taper for COPD flare (completed yesterday)
Losartan 50 mg PO daily
Metoprolol 50 mg PO BID
Paroxetine 20 mg PO daily
Quetiapine 200 mg PO BID
Lipitor 20 mg PO QD
Multivitamin PO daily
Iron sulfate 325 mg PO BID

Review of Systems:
Constitutional: Negative for diaphoresis. Negative for fever/chills. Has fatigue, denies insomnia. Appetite is good.
HENT: Negative for ear pain/tinnitus, postnasal drip, rhinorrhea, sinus pain, sinus pressure or sore throat. Eyes: negative for pain/discharge/visual changes.
Respiratory: Negative for cough. Negative for shortness of breath/chest tightness. Negative for wheezing.
Cardiovascular: Negative for chest pain. Negative for palpitations. Negative for syncope.
Endocrine/hematology: negative for heat/cold intolerance. Negative bleeding. Some bruising on her right thigh from surgery. Small bruise on her right knee.
Gastrointestinal: Negative for abdominal pain. Negative for N/V. Negative for blood in stool. Negative for diarrhea. Has constipation occasionally.
Musculoskeletal: her right hip feels a little stiff still. Pain is ok.
GU: Negative for dysuria/frequency/blood in urine. Negative for retention.
Skin: Negative for rashes/lumps/bumps/surgical wound on right hip.
Neurological: Negative for dizziness, numbness/tingling. Headaches.
Psychiatric/Behavioral: depression is ok.

Physical Exam:
BP 138/70, Pulse 72, Temp 98.6 F, R 18, SpO2 92%, Wt 125 lb., H 5’8”, BMI 19.0

Constitutional: She is oriented to person, place, and time. She appears well-developed and well-nourished.

HENT: Head: Normocephalic, atraumatic.
Right Ear: TM is visible and intact. Appears normal, pearly gray color. Left Ear: TM is visible and intact. Appears normal, pearly gray color.
Nose: mucosa looks moist and pink.
Eyes: Conjunctivae and EOM are normal. Pupils are equal, round, and reactive to light.
Neck: Neck supple. No thyromegaly noted. No lymphadenopathy noted.
Cardiovascular: Normal rate and regular rhythm. No murmur, rub or gallops noted.
Pulmonary/Chest: Effort normal and breath sounds diminished. Lungs are clear to auscultation. No wheezing.
Abdominal: Soft. Bowel sounds are normal.
Neurological: She is alert and oriented to person, place, and time. She has normal reflexes.
Skin: Skin is warm and dry. Surgical wound to her right hip looks great, healing, edges approximated. Sutures are out. The wound is open to air. There is slight bruising and edema to the area. No signs of infection.
Right leg: sensation is intact and pulses (popliteal, posterior tibial and dorsalis pedis) are palpable and equal. Movement of the hip remains slightly restricted because of the surgery and pain.
Psychiatric: She has a normal mood and affect. Her behavior is normal. Judgment and thought content normal.

Assessment and Plan:
M80.051 Age-related osteoporosis with current pathological fracture, right femur
F17.200 Nicotine dependence
I10 Hypertension
E78.00 Hypercholesterolemia
J44.9 COPD
F32.1 depression

Will focus on post-hospital discharge and osteoporosis management today and I will highlight some of the things I would address with Mary in following visits. I do not want to overwhelm her with too much information today. Labs ordered: BMP, CBC. Imaging ordered DXA scan.

Post-hospital discharge: will order CBC since she is feeling tired, she is status post-surgery and has history of anemia.
Osteoporosis: will order kidney function test and calcium levels (BMP). If all ok and given that she has osteoporosis, had recent fracture, she is a smoker, she is on daily inhaled corticosteroids and intermittent oral steroids, will start her on Alendronate 70 mg PO weekly. Take on empty stomach with a full glass of water. Do not lay down for 30 min to an hour after taking the medication. Do not eat or take other medications with alendronate, wait at least 30 min. Side effects: bone, joint or muscle pain, nausea, difficulty swallowing, heartburn, irritation of the esophagus and gastric ulcer. Severe adverse effects osteonecrosis of the jaw, atypical femur fracture and esophageal cancer. I reassured her that these are rare and normally associated with high doses and long-term use of bisphosphonates, normally over 10 years with alendronate. Will start her on calcium 1,200 mg daily + vitamin D 1,000 IU daily as well.

Fall prevention education included: no lose rugs at home, grab bars in the bathroom, well-lit rooms. Weight bearing exercises, as well as balance exercises. Make sure you know where your little dog is before walking. Use your walker until you are discharged from its use.
Bone health: smoking cessation, exercise, calcium and vitamin D supplement. Try to stay away from steroids.

She agreed to pneumonia vaccination (PPSV23) today. Does not want the new Shingrix vaccine.

I will see her in one month follow up for establishing care labs or she can return to the clinic if new concerns or problems manifest before that time.
1 year follow up for osteoporosis will repeat a DXA scan to monitor BMD and will assess fracture risk with FRAX. Will have her taking alendronate for 3-5 years depending on response to therapy. She agreed with plan.

Following visits:
Smoker: For Mary I suggested lung cancer screening, she refused. I offered tobacco cessation services, she said she will think about it. Will emphasize the relationship between smoking and COPD exacerbations and will educate her about detrimental effects of smoking on bone health. We can talk more about it on the next visit.
COPD: she says that this is well controlled right now with her inhaler. Will talk more about COPD maintenance during next visit.
Hypertension: well controlled with metoprolol and losartan. Will check urine microalbuminuria next visit.
Hypercholesterolemia: will order lipid panel and hepatic panel for next visit.
Anemia: She is on Iron sulfate. She says she is feeling tired. Will check CBC.
Depressions: well controlled with paroxetine and quetiapine.

Other screening suggestions: colonoscopy, she does not want to have another done, had a colonoscopy 5 years ago, no polyps found. Will talk about FOBT on next visit. Mammogram: she had a mammogram 5 years ago. We may suggest one last mammogram before she turns 74. Previous were normal, no history of breast cancer in her family, she is a smoker.

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Literature Review

In evaluating an osteoporosis treatment plan for the patient in the case study, the literature was reviewed using CINAHL, PubMed, MEDLINE and Cochrane Library via the Harley French Library at the University of North Dakota. The search terms used included "bisphosphonate", "duration", "osteoporosis", "cessation", "drug holiday". Results were limited to English language, human studies, bisphosphonates in the treatment of osteoporosis and publish date after 2013. This resulted in 110 articles. Twelve articles were retained (5 systematic reviews, 4 randomized controlled trials and 3 peer-reviewed journal articles) based on abstract review and on their ability to aid in care planning for patients with post-menopausal osteoporosis. New prospective studies evaluating the benefits and risks of bisphosphonate therapy are limited. A popular literature search was also conducted to inquire about the mechanisms of action of bisphosphonates, the prevalence of osteoporosis in the aforementioned population and the costs associated with fractures related to low BMD.

Ultimately, the review of the literature should help the author of this paper to select an adequate BP drug for the patient in the case study, guide her on how to monitor patient status and success of therapy, and help her to define duration of the therapy (addressed on the plan described in the case study).

Prevalence and Cost of Osteoporosis

Osteoporosis and the related fractures are costly. A study done by Wright et al. (2014), estimated that among the older population (>50 years old) in the USA, osteoporosis and osteopenia are prevalent in approximately 53.6 million people, with women and non-Hispanic whites being the most affected. In terms of costs, low BMD-related fractures have been evaluated at $19 billion per year and calculated to increase up to $25.3 billion by 2025 (National

Osteoporosis Foundation, 2015). Although not the focus of this paper, it is worth noting that screening should be a clinician's priority when taking care of post-menopausal women.

Bisphosphonates

Given that osteoporosis represents a major risk for broken bones with the associated increase in morbidity, mortality and public health burden, medications have been developed to manage this condition. Bisphosphonates are considered safe and effective for the treatment of osteoporosis in post-menopausal women. Studies have shown that these medications are able to reduce vertebral fractures (40-70%), hip fractures (20-50%) and nonvertebral fracture (15-39%) (Adler et al., 2016). The numbers speak clearly about their efficacy. Bisphosphonates approved by the FDA for the prevention and treatment of osteoporosis in post-menopausal women are alendronate, zoledronate, risedronate and ibandronate (American Bone Health, 2019). They belong to the drug class called pyrophosphate analogues. They work by inhibiting bone resorption by the osteoclasts. They show a strong chemical likeness for bone tissue giving them a long half-life within the skeleton. Because of this particular characteristic, BP accumulate on bone surface allowing these drugs to provide residual treatment and to continue to inhibit osteoclast activity, even after discontinuation of therapy has occurred (Meier et al., 2017). Their affinity for bone varies from drug to drug being zoledronate the BP with the longest half-life, followed by alendronate, ibandronate and risedronate in order of decreasing affinity (Diab & Watts, 2013).

Risks Associated with the use of Bisphosphonates

Unfortunately, as any other medication, bisphosphates are not free of side effects, and their remanent activity can be good or bad. Recently, concerns about severe side effects associated with the intake of bisphosphonates have emerged. The most severe adverse effects

associated with the intake of BP are ONJ, AFF and esophageal cancer (Villas, Giannakos & Lane, 2015). According to Villas et al. (2015), the association of ONJ and bisphosphonates therapy exists. This rare condition has been observed in patients taking bisphosphonates for 4 years or more. Nevertheless, the causation cannot be proven given that ONJ has been found in patients who are not taking these medications. In regard to AFF, the conclusions are similar. The association of BP with AFF has been observed in treatment duration of near 10 years, yet, causality has not been established. For esophageal cancer, the malignancy was observed in patients who had more than 10 bisphosphonate prescriptions. In another important study Adler et al., (2016) found that the incidence of ONJ was 1/10,000 to 1/100,00 and in those who developed the condition while taking bisphosphonates, this was mild and went away with conservative treatment or without it. This study noted some of the risks associated with the development of ONJ as well. To mention poor oral hygiene, smoking, diabetes mellitus, related use of medications such as glucocorticoids and/or chemotherapy drugs, and invasive dental procedures (i.e. implants, extractions). For the incidence of AFF, this same study found that 1.8 patients out 100,000 per year developed AFF after a 2-year exposure to bisphosphonates versus 113 patients out of 100,000 with 8 to 9.9 years of exposure. These results support the fact that AFF incidence increases with prolonged bisphosphonate therapy. Meier et al. (2017), found similar results and calculated the incidence of ONJ to be 0.01% to 0.025% with increasing numbers as treatment duration lengthens. This investigation also calculated a low risk of AFF ranging from 3.2 to 50 cases per 100 000 person-years. Neither Adler et al. nor Meier et al. evaluated the incidence of esophageal cancer among patients taking BP. It is important to note that FDA has not enforced package labeling with warnings for esophageal carcinoma while on BP therapy (Adler et al., 2016).

These statistics should be compared to the higher prevalence of fractures in patients with low BMD. A Recent survey done by the National Osteoporosis Foundation (2017) indicates that 1 in 2 women over the age of 50 will sustain a fracture related to low BMD. In spite the fact that ONJ, AFF and esophageal cancer are severe and concerning side effects for patients and providers, their occurrence is rare while the prevalence of fractures among women with osteoporosis is high. Treatment with bisphosphonates should not be dismissed. The patient in the case study would benefit from BP therapy.

Other adverse effects linked to the intake of bisphosphonates are atrial fibrillation, kidney damage and acute gastrointestinal intolerance. Currently, the FDA appraises the association between atrial fibrillation as weak. To protect kidney function, BP should not be prescribed for those with creatinine clearance below 30-35 ml/min. For those patients with gastrointestinal intolerance intravenous bisphosphonate should be considered (Adler et al., 2016).

Duration of Therapy

New studies evaluating BP and their associated risks are limited and recommendations on duration of treatment remain evasive. There are 3 important studies done in the past. These studies are still considered relevant today and bone health organizations such as the National Osteoporosis Foundation (NOF), the American Association of Clinical Endocrinologists (AACE) and the American Society for Bone and Mineral Research (ASBMR) have written recommendations based on these studies to aid the clinician in the management of patients with low BMD. These classic studies are the FIT-FLEX study, the HORIZON and its extension trial, and the VERT-MN study (Lee et al., 2015). In the FIT-FLEX study, alendronate was evaluated. The authors compared 5 years of therapy versus 10 while investigating the effects of alendronate on BMD, bone turn over markers (BTM) and fracture risk. The study found no

difference between the two groups. It is worth to note that post hoc analyses observed that for those with a femoral neck T-score of < -2.5, longer treatment with alendronate reduced risk of non-vertebral fractures in 50% of the cases (Reid, 2015). In the HORIZON study and its extension trial, zoledronate was evaluated during a 3-year treatment period versus 6 years. The study yielded similar results to the ones in the FIT-FLEX study. There was no difference in fracture risk between the group who received treatment with zoledronate for 3 years versus the group who receive treatment for 6 years. Yet, they noted that those who received treatment for a longer period had more stable BMD and BTMs compared to the subjects who received zoledronate for only 3 years. The authors concluded that for those individuals with high risk of fractures, longer treatment with zoledronate may be appropriate (Villa, Gianakos, & Lane, 2016). Nevertheless, Adler et al. (2016) in their extensive research suggested that the association between stable BMD or BTM and lower fracture risk is weak. In the VERT-MN study, risedronate was evaluated to seven years. The study showed a significant reduction in the risk of vertebral fractures (65%) (Schneider, 2015). In a follow up study, Black et al., (2014) conducted a 3-year, multicenter, randomized, double blind, second extension study of the HORIZON trial to evaluate the benefits of treatment extension with zoledronate from 6 years to 9 years. The study did not show any evidence of better BMD, BTMs or reduction of fracture risk. Interestingly, the investigators observed a small increase in cardiac arrhythmias with treatment duration of 9 years. They concluded that treatment with zoledronate should stop at the sixth year of therapy, and stated that residual activity of zoledronate remains for 3 additional years after cessation of BP intake.

International studies have been also conducted to evaluate BP therapy and to review current recommendations. A retrospective cohort study done in Taiwan was conducted in a

population of 1342 women with a mean age of 71 over a period of 10 years, to evaluate the effects of continuing alendronate therapy to reduce fracture risk beyond the standard 5 year-therapy. The study found no additional benefits in continuing therapy beyond this time. The investigators did not have data in order to assess any changes in BMD of the population studied, however. Interestingly the study did not find changes in fracture risk among patients who were not completely compliant with BP intake, given the long half-life of these medications, and concluded that a gap of up to 18 months should not affect fracture risk. They did not observe any AFF during the course of the investigation (Wang, Lu, Dusetzina & Wu, 2016). The Swiss Association against Osteoporosis (2017) has also established guidelines based on current recommendations, to manage osteoporosis. They suggest that oral BP therapy should be prescribed for 5 years while intravenous therapy for only 3. Patients monitoring is warranted with DXA scan every 2-3 years. Patients should be classified as low or high risk. Those at low risk for fracture can stop bisphosphonate and should be encouraged to maintain bone health with calcium and vitamin D supplements. High risk patients should continue with therapy but switched from bisphosphonates to another type of medication such as denosumab (human monoclonal antibody) (Meier et al., 2017). Finally, in a Japanese study, ibandronate was evaluated. The investigators suggested that therapy for five years was considered adequate and patient should be re-evaluated after 1-2 years after withdrawal from therapy (Hagino et al., 2014).

In summary, duration of treatment should be up to 5 years with oral bisphosphonates and up to 3 with intravenous bisphosphonates. Patients who after therapy are at low risk of fracture can stop treatment, while those who remain at moderate to high risk may benefit from continuous oral BP therapy for up to 10 years or up to 6 years with intravenous BP therapy. For those

patients who continue with treatment monitoring for severe side effects is essential. Clinicians should re-assess patient status in those who present with thigh or groin pain especially in the absence of trauma. This symptom has been associated with AFF. Therapy with bisphosphonate should be discontinued, imaging should be obtained and consultation with orthopedics placed in this case (Reid, 2015). This is an important patient education fact.

Drug Holiday

A *Drug holiday* is a concept that emerged as a method to take advantage of the benefits of a drug while minimizing the risk of severe adverse effects associated with its long-term use. Lee et al., (2015) conducted a South Korean Study in which a *drug holiday* is proposed for the management of low risk patients with osteoporosis. The authors in this study created a simple algorithm for patients on alendronate, risedronate and zoledronate. A drug holiday should be offered after 5 years for those on alendronate and risedronate, and after 3 years for those on zoledronate. Annual assessment of the patient's risk fracture should be conducted with measurements of BMD. Re-initiation of therapy should be established if patient declines in bone health (i.e. T-score ≤-2.5, new osteoporotic fracture). The FDA agrees to drug holidays but warns that high risk patients may benefit from continuation of therapy with BP or non-BP drug (Diab & Watts, 2013).

On the other hand, if the patient is considered at high fracture risk, normally defined as those who have a T-score of < -2.5, have had a fracture and have secondary osteoporosis due to medications and comorbidities, continuation of therapy or switching to a different treatment should be offered.

A French retrospective cohort study done to evaluate the effects of *drug holiday* with alendronate, risedronate, zoledronate and ibandronate in a population of women with

osteoporosis, showed that after cessation of therapy and within a period of 6 to 36 months the risk of fractures increased to 40% (Legroux, Cortet, Paccou, Mignot & Taisne, 2017). The study was small, however.

As a general rule the length of a *drug holiday* should be instituted according to the bone tissue affinity of the drug, and re-evaluation of the patient status should be done in 1-2 years after cessation of alendronate, ibandronate and risedronate and in 2-3 years after cessation zoledronate (Diab & Watts, 2013).

Patient Monitoring

Guidelines on how to monitor treatment with BP are not clear. DXA scan is the most widely used tool for monitoring BMD. Some literature suggest that monitoring can be done with measurements of BTMs such as bone alkaline phosphatase, osteocalcin, C-terminal propeptides of type I collagen (CTX) and NTX. Urine bone resorption markers include breakdown products of type I collagen such as pyridonium cross-links (PYR and D-PYR) (Khalid & Krum 2016). Limited studies have been conducted to assess the accuracy of bone health monitoring. One of those studies is an investigation conducted by Bauer et al. (2014), this was prospective study to follow the placebo patients from the FLEX investigation. They wanted to evaluate methods to better assess fracture risk in patients with low BMD after stopping treatment with alendronate. The study concluded that a better prediction of fracture risk is done by noting the age and BMD at the hip at cessation of therapy rather than with yearly DXA scans or BTMs.

Important organizations have tried to write guidelines. The ASBMR (2016) recommends that after 5 years of oral BP or 3 years of intravenous BP, re-assessment of patient's risk should be considered. Nevertheless, the ASBMR fails to recommend a method given that studies have not shown that measurement of BMD, BMTs or fracture-risk assessment such as with the World

Health organization FRAX tool, are able to accurately predict fracture risk among patients with osteoporosis (Adler et al., 2016). On the other hand, the AACE and the American College of Endocrinology (ACE) (2016), recommend that monitoring of the patient's bone health should be done with DXA scan every 1-2 years until stable, meaning there is an increase in BMD and absence of new fractures. Clinicians may use BTMs to monitor patient's compliance with therapy and effectiveness of therapy as well.

Finally, the NOF (2014), proposes that measurement of height and measurement of BMD with DXA scan are essential for therapy evaluation. This should be done after one year of initiation of therapy and one to two years after that. BTMs can be used as a secondary tool to assess the effects of treatment.

In summary, assessment of patient status and efficacy of therapy can be done using different tools, being the most relevant the incidence of new fractures.

Learning Points.

-Bisphosphonates are effective in the treatment of osteoporosis and in the reduction of risk of fractures in post-menopausal women. Each bisphosphonate has a different half-life therefore duration of treatment, drug holiday and interval of patient monitoring should be established according to the particular characteristics of the drug.

-Adverse risk effects such as ONJ and AFF are rare and have been observed with high doses of and/or long-term treatment with bisphosphonates.

-All patients should be offered a drug holiday. High risk fracture patients may be better off with continuation of BP therapy or switching to a non-bisphosphonate anti-osteoporosis drug. Treatment should be individualized and should incorporate patient preferences and clinician judgement.

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