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Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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Objectives

After completion of this program, the reader should be able to:

1. Identify the characteristics, pathophysiology and prevalence of osteoporosis.
2. Recognize patients at risk for or suffering from glucocorticoid-induced osteoporosis.
3. Define the mechanism, efficacy and safety of alendronate, risedronate, zoledronic acid and teriparatide.
4. Identify appropriate treatment plans based on the FRAX score, risk level and glucocorticoid therapy of the patient.
5. Recognize the unique advantages of individual therapies and apply them to patient cases.
6. Describe the role of a pharmacist in preventing and managing glucocorticoid-induced osteoporosis.

Abstract

Osteoporosis is a disease state resulting in decreased bone mineral density (BMD) and increased risk of fracture, specifically of the vertebrae, spine and hip. Risk factors and high risk populations for developing osteoporosis include low BMD, long-term glucocorticoid therapy, genetics, diet, postmenopausal women and patients with inflammatory or chronic disease states. A variety of signaling pathways involving hormones, cytokines and other signaling molecules are involved in bone formation and are affected by long-term glucocorticoid therapy, leading to the development of glucocorticoid-induced osteoporosis (GIO).

There are a variety of drugs that work efficaciously to prevent and treat GIO. Alendronate is a potent bisphosphonate that has shown efficacy in increasing BMD and decreasing bone turnover. Risedronate, another potent bisphosphonate, has demonstrated similar effects in patients suffering from GIO and has been observed to decrease fractures. Zoledronic acid is another bisphosphonate option that has proven efficacy and noninferiority to oral bisphosphonates in GIO, but it is unique in that it is given intravenously once a year. Additionally, teriparatide is a recombinant human parathyroid hor-

mone (PTH) which is a newer therapy for the treatment of GIO and is beginning to replace older therapies such as testosterone and estrogen. The once daily administration of teriparatide induces bone formation, which allows for increase in bone mass thus reducing the risk of vertebral and nonvertebral fractures. Furthermore, calcium and vitamin D are usually seen as prophylaxis and adjunctive therapy. At the initiation of therapy, pharmacists should recommend bone density tests to evaluate if medication is appropriate for the patient. Subsequent action includes patient education and monitoring of initiated therapy and disease progression.

Key Terms

Alendronate; Bone Density; Bone Remodeling; Chronic Disease; Osteoblasts; Osteogenesis; Osteoporosis; Parathyroid Hormone; Risedronate Sodium; Risk Factors; Teriparatide; Vitamin D

Introduction to Osteoporosis

Osteoporosis is characterized by the presentation of low bone density which may be caused by a variety of factors.¹ Clinically, osteoporosis affects the normal daily activities and quality of life of patients who suffer from this disease. Quality of life is affected through the increased risk of fracture in areas such as the hip, vertebrae and wrist. These complications can ultimately lead to significant morbidity and mortality. Common risk factors for osteoporosis include low bone mineral density (BMD), long-term glucocorticoid therapy and diet. Populations most affected by osteoporosis include postmenopausal women, patients with inflammatory and chronic diseases and patients currently taking long-term glucocorticoid therapy.² Symptoms of osteoporosis most commonly include an increase in fractures (specifically of the vertebrae, spine and hip) and bone loss detected through BMD testing.

The pathophysiology of osteoporosis is a complex process involving a variety of cells. It is suggested that bone remodeling plays a large role in the pathophysiology of osteoporosis.³ The processes of bone resorption and deposition, collectively termed bone remodeling, are dependent upon the activity of osteoclasts and osteoblasts. Osteoclasts transport protons to the extracellular space resulting in a lowering of pH and, therefore, dissolving bone mineral. Osteoblasts deposit bone mineral, although their mechanism is still not fully understood. These cells communicate to regulate bone remodeling. Hormones also play a large role in the regulation of osteoblasts and osteoclasts and are necessary for bone maintenance and development. In osteoporosis, complex interactions among cytokines, hormones, pH, osteoblasts and osteoclasts cause osteoblasts to release signaling molecules that induce osteoclasts to dissolve bone. This ultimately

leads to decreased BMD and development and progression of osteoporosis.

In a global longitudinal study of regional differences in the treatment of osteoporosis, several gaps in treatment became evident. In the United States alone, only 52 percent of patients who reported prior fractures of the hip or spine received treatment with an anti-osteoporotic medication.¹ Of patients diagnosed with osteoporosis, only 62 percent receive treatment. Although this seems low, compared to other countries women in the United States are three times more likely to be treated for osteoporosis.

Pharmacology of Glucocorticoid-Induced Osteoporosis

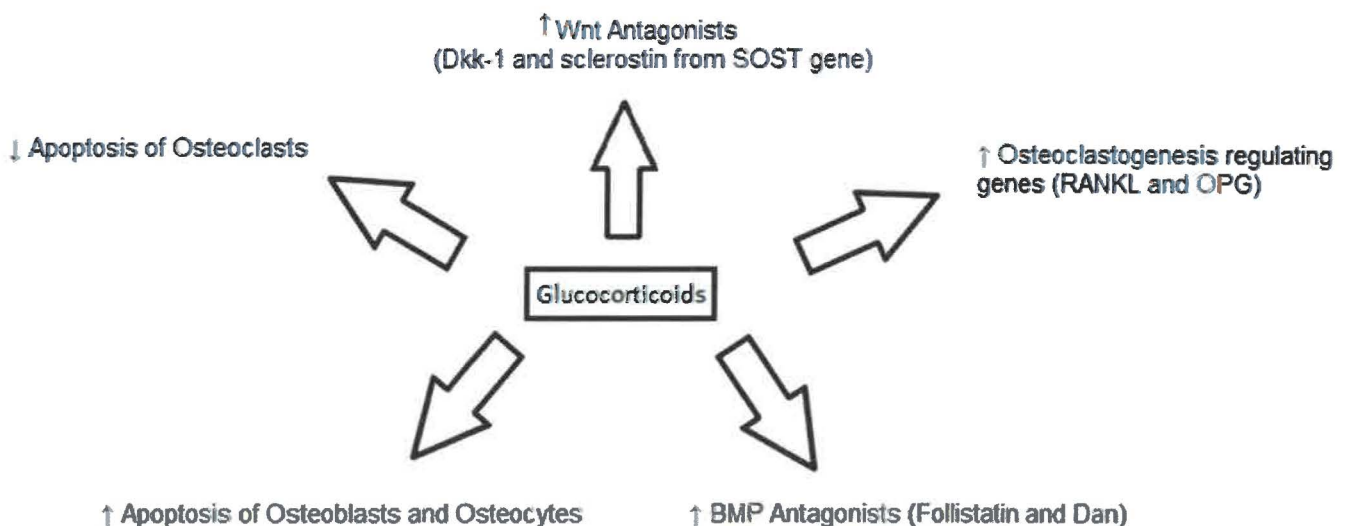
The mechanisms in which glucocorticoids affect the bone to induce osteoporosis are complex, multifaceted and still not completely understood (Figure 1). One of the known pathways involved in glucocorticoid-induced osteoporosis (GIO) is the Wntless-type mouse mammary tumor virus integration site family member (Wnt) signal pathway which has a role in osteogenesis and the differentiation of osteoblasts.^{4,5} Researchers have examined an antagonist of this pathway, dickkopf-1 (Dkk-1). By testing cultured human osteoblasts, Ohnaka and colleagues found that when given dexamethasone there was an increased expression of Dkk-1 in the osteoblast through the activation of transcription of the Dkk-1 promoter by glucocorticoids. Because the glucocorticoids upregulate expression of Dkk-1, they ultimately antagonize the Wnt signaling pathway, interfering with osteoblast signaling for bone formation. A study conducted by Hayashi and colleagues looked at the expression of certain mRNA proteins in an osteoblastic precursor cell line when affected by dexamethasone.⁶ This study showed an increase in a different Wnt signal inhibitor, axin-2, along with an increased expression in bone morphogenetic protein (BMP) antagonists, follistatin, and Dan. Similar to the Wnt pathway, BMP stimulates osteogenesis and osteoblast differentiation in bone. Howev-

er, the expression of follistatin and Dan suppresses proper osteoblast function. There was also a decrease in Runx2, a known downstream protein of the BMP pathway, providing additional evidence that dexamethasone inhibits the pathway.

Glucocorticoids also increase the apoptosis of osteoblasts and osteocytes while decreasing the production of osteoclasts.⁷ A study conducted by Weinstein and colleagues showed mice in the high-dose prednisolone group (2.1 mg/kg/day) had a significant increase in osteoblast apoptosis in the vertebral cancellous bone compared to controls (2.03 +/- 0.34 vs. 0.66 +/- 0.07 percent, $P < 0.05$). Apoptotic osteocytes were also found in cortical bone sections taken from the femora, in contrast with the absence of apoptotic osteocytes in the control group.

The newest research suggests that glucocorticoids may cause osteoporosis by a different mechanism by activating the local renin-angiotensin system in bone.⁸ In a study by Yongtao and colleagues, rabbits were treated with dexamethasone alone or with perindopril, an angiotensin-converting enzyme (ACE) inhibitor. The study found that several genes and proteins including the sclerostin (SOST) gene, the receptor activator of nuclear factor- κ B ligand (RANKL) to osteoprotegerin (OPG) ratio, and Runx2 were influenced. The SOST gene is responsible for the production of sclerostin, which antagonizes the Wnt pathway. The RANKL/OPG ratio increases osteoclastogenesis (higher ratio levels mean more osteoclastic genes found in mRNA). When treated with dexamethasone alone, SOST and RANKL/OPG levels were increased, but in the dexamethasone plus perindopril group, SOST and RANKL/OPG were significantly lower compared to the dexamethasone alone group. Runx2 was decreased when given with dexamethasone alone, but it was increased when given with perindopril. This coincides with the results from the aforementioned study by Hayashi and colleagues. The effects

Figure 1. Summary of Glucocorticoid Effects on Bone.^{4,6,7,8}



The increases in Wnt and BMP antagonists interfere with osteoblast signaling ultimately inhibiting osteogenesis.

of the glucocorticoid were reversed when given an ACE inhibitor. Therefore, the study concluded that the local renin-angiotensin system on bone plays a role in GIO, and further studies are needed to fully understand this mechanism.

Pharmacologic Treatments for Osteoporosis

Bisphosphonates

Bisphosphonates have shown promise as effective therapy in GIO because of the ability of this drug class to inhibit the resorption of bone while having minimal side effects, thus making therapy more desirable for the patient.⁹ Bisphosphonates work to increase BMD by inhibiting bone resorption and the activity of osteoclasts. Although there are many bisphosphonates, three are particularly recommended by the American College of Rheumatology for the treatment of GIO: alendronate, risedronate and zoledronic acid.¹⁰

Alendronate

Alendronate is a potent second-generation bisphosphonate.⁹ Alendronate has a high affinity for bone mineral and is taken up into bone during osteoclast resorption. The drug inhibits the enzyme farnesyl pyrophosphate synthase which is an enzyme involved in the mevalonic acid pathway.¹¹ The mevalonic acid pathway affects the production of isoprenoids essential for the modification of small guanosine triphosphate (GTP) binding proteins. By inhibiting this pathway, alendronate restricts osteoclast survival. It has also demonstrated effectiveness in increasing BMD of the hip and spine as well

as decreasing the incidence of fractures in these areas, along with the forearm, in postmenopausal women who suffer from osteoporosis.¹²

The American College of Rheumatology's guidelines for alendronate therapy suggests determining the patient's risk category based on their Fracture Risk Assessment Tool (FRAX) score.¹⁰ The FRAX is a questionnaire tool used to assess a patient's risk of fracture within the next 10 years in patients who are not being treated and are between the ages of 40 years and 90 years.¹³ It can be used with or without knowledge of the individual patient's BMD in low, medium and high risk patients. Additionally, there is a strong level of evidence for the efficacy and use of alendronate in therapy. Please refer to Table 1 for specific recommendations. At all risk levels, patient monitoring is recommended. The pharmacist should monitor for additional fractures, modifiable patient risk factors for osteoporosis, patient adherence to therapy and changes in BMD.¹⁰ If glucocorticoid therapy is discontinued alendronate may also be discontinued.

Typically, alendronate is dosed once daily, twice weekly or once weekly. Each regimen has shown near equivalent efficacy in increasing BMD in the hip, neck, trochanter and entire body.⁹ It is recommended as a once daily regimen in patients with GIO receiving systemic steroids. Typically, patients are given 5 mg by mouth daily. In women who are postmenopausal not taking any type of estrogen replacement therapy,

Table 1. Recommendations for Therapeutic Use in Glucocorticoid-Induced Osteoporosis.¹⁰

Glucocorticoid Therapy	Low Risk Patient (FRAX < 10% for 10 year major osteoporosis fracture)	Medium Risk Patient (FRAX 10-20% for 10 year major osteoporosis fracture)	High Risk Patient (FRAX >20% for 10 year major osteoporosis fracture)
< 5 mg/day for ≤ 1 month			Alendronate Risedronate Zoledronic Acid
≥ 5 mg/day for ≤ 1 month			Alendronate Risedronate Zoledronic Acid Teriparatide
Any dose for 1-3 months			Alendronate Risedronate Zoledronic Acid
< 7.5 mg/day for ≥ 3 months		Alendronate Risedronate	Alendronate Risedronate Zoledronic Acid Teriparatide
≥ 7.5 mg/day for ≥ 3 months	Alendronate Risedronate Zoledronic Acid	Alendronate Risedronate Zoledronic Acid	Alendronate Risedronate Zoledronic Acid Teriparatide

These recommendations are from the American College of Rheumatology and apply to postmenopausal women and men over the age of 50 years.

10 mg by mouth daily is recommended. Patients should remain sitting upright for at least 30 minutes after taking each dose to avoid esophageal irritation. Bone mineral density should also be measured at baseline, six months and 12 months. Due to the potential for increased risk of osteonecrosis of the jaw, patients on glucocorticoids should be advised to have dental exams prior to initiation of bisphosphonates like alendronate. Patients should also have their renal function and serum calcium levels checked before initiation. If the creatinine clearance is less than 35 mL/min, alendronate should not be started. Furthermore, because alendronate decreases serum calcium levels, hypocalcemia should be corrected before starting therapy, and calcium levels should be monitored throughout therapy. This medication should be used with caution in patients suffering from certain gastrointestinal (GI) and esophageal diseases such as esophagitis, gastritis and gastroesophageal reflux disease due to the increased risk of esophageal irritation associated with this therapy. The geriatric population is at increased risk for these reactions and should be monitored for any sign of GI reactions. Also, this medication is specifically contraindicated in patients with an increased risk of aspiration or delay of emptying of the esophagus. Lastly, therapy should be discontinued if the patient develops any signs of dysphasia or retrosternal pain.

In a study conducted by Saag and colleagues, researchers found that alendronate increased BMD in patients currently taking glucocorticoid therapy.¹² The main goal of the study was to examine the mean percent change in lumbar-spine bone density from baseline to week 48 between the groups receiving different doses of alendronate therapy and placebo. Secondary outcomes measured bone density changes in the hip along with new fracture incidence of the vertebrae and bone turnover markers. The study was a double-blind, randomized, placebo-controlled, multicountry trial. Two different doses of alendronate were studied in men and women ranging from 17 to 83 years of age without significant differences in baseline characteristics. Patients had been receiving at least 7.5 mg of prednisone daily or an equivalent glucocorticoid therapy for underlying chronic diseases. They were then further divided based on the duration of their glucocorticoid therapy (four months, four to 12 months and more than 12 months).

The study included 477 patients who were randomly assigned to receive 5 mg or 10 mg alendronate or matching placebo daily.¹² The patients were seen at baseline, four, 12, 24, 36 and 48 weeks where researchers reviewed their therapy usage diary. At baseline and every 12 weeks, BMD of the hip, lumbar area of the spine and whole body were quantified and analyzed. Studies were evaluated using intention-to-treat standards. Results were analyzed using the step-down Tukey trend test which adjusted for multiplicity.

After 48 weeks of therapy, patients receiving 5 mg and 10 mg of alendronate saw a significant increase ($p < 0.001$) in the BMD of the neck, trochanter and lumbar spine.¹² Only 45 percent of the patients in the placebo group saw an increase in

the lumbar spine BMD as compared to 80 percent in the treatment group (mostly seen in postmenopausal women). Whole body BMD significantly increased in the treatment group on 10 mg of alendronate therapy. Similar side effects were experienced among groups such as headache, musculoskeletal pain and upper respiratory infection. Patients receiving 10 mg of alendronate reported increased GI adverse events.

This study concluded that alendronate was efficacious in increasing the BMD in patients with GIO regardless of duration of glucocorticoid therapy.¹² Additionally, bone turnover was decreased as a result of this therapy.

Risedronate

Risedronate, one of the most potent bisphosphonates, acts by inhibiting the resorption of bone but does not affect mineralization.¹⁴ The action of risedronate is based on its affinity for the component of bone matrix hydroxyapatite.¹⁵ It acts as an analogue of isoprenoid diphosphate lipids, therefore inhibiting farnesyl pyrophosphate, a key enzyme associated with the mevalonate pathway. By inhibiting the key enzyme in osteoclasts that is essential for the synthesis of isoprenoid lipids, posttranslational modification of small GTPase proteins is inhibited. As a result, osteoclast activity is inhibited, and bone resorption and turnover are reduced. Also, postmenopausal women have seen a net gain in bone mass with treatment of risedronate.¹⁶

The American College of Rheumatology's guidelines for risedronate therapy are evaluated in the same manner as alendronate.¹⁰ Please refer to Table 1 for recommendations on initiation of treatment of risedronate based on FRAX score and glucocorticoid therapy. At all risk levels, patient monitoring is recommended. Additionally, risedronate has a strong level of evidence in low, medium and high risk patients.

Risedronate is typically dosed once daily, once weekly, once monthly or twice monthly depending on the condition.¹⁴ For GIO, it is a recommended dosing of 5 mg orally daily before breakfast in an immediate-release tablet. Patients should remain sitting upright for at least 30 minutes after receiving each dose to avoid esophageal irritation. This drug is contraindicated in patients with hypocalcemia or abnormalities of mineral or bone metabolism such as chronic kidney disease and certain thyroid disorders. It has been shown to cause skin reactions such as rash and induce acute bronchospasms in patients with hypersensitivities to phosphonate or aspirin-sensitive asthma. Similar to alendronate, risedronate should not be used in patients unable to remain sitting upright for 30 minutes after receiving a dose of medication or those who have esophageal malfunctions. Monitoring should occur for symptoms of esophageal reactions, dysphasia or retrosternal pain.

In a multicenter, double-blind, placebo-controlled, parallel-group study conducted by Reid and colleagues, researchers aimed to assess the efficacy and safety of risedronate in pa-

tients taking high dose, long-term glucocorticoid therapy.¹⁶ Patient tolerability of this therapy was also assessed. Male and female patients between the ages of 18 years and 85 years were enrolled from 23 study centers and had been receiving at least 7.5 mg of glucocorticoid therapy for a minimum of six months. A total of 290 patients were enrolled (109 men and 181 women), and 14 percent of the women were premenopausal. Patients were divided into three groups: men, premenopausal women who were either sterile or using some kind of contraceptive and women who were postmenopausal for a year or more. Patients were then randomized to receive placebo, 2.5 mg risedronate or 5 mg risedronate daily for one year. Baseline demographics and characteristics were comparable among treatment groups. Patients were required to take the medication with 240 ml of water 30 to 60 minutes before breakfast on an empty stomach and to remain upright for at least one hour. Additionally, patients received vitamin D and calcium supplementation. The study had 90 percent power to detect a difference in BMD with an alpha level of 0.05 and standard deviation of 5 percent.

The BMD of the lumbar spine, neck, trochanter and forearm were measured at baseline, six months and 12 months.¹⁶ Vertebral fractures were also assessed at baseline and 12 months. Physical examination of the patients was conducted at six months and 12 months, and laboratory tests were completed at baseline, one month, three months, six months and 12 months. After 12 months of treatment, risedronate demonstrated significant differences in BMD of the lumbar spine ($p < 0.001$), femoral neck ($p < 0.004$) and trochanter ($p < 0.001$). Patients receiving the 5 mg dose of risedronate saw an increase in BMD by 2.9 percent in the lumbar spine, 1.8 percent in the femoral neck and 2.4 percent in the trochanter. In patients receiving 2.5 mg of risedronate, there was a small increase in spinal BMD which was not significant when compared to the placebo group. In the radius, BMD was maintained in patients receiving 5 mg risedronate, while there was a loss of BMD in the placebo group. A further subgroup analysis of patients receiving 5 mg risedronate demonstrated that 5 mg therapy, relative to placebo, increased the BMD at all sites in both men and postmenopausal women. Due to the small population of premenopausal women in the study, their results were not considered significant. Risedronate 5 mg therapy was also shown to increase BMD in patients with underlying chronic disease (rheumatoid arthritis, lung disease). Although these results were not statistically significant, there was a positive correlation.

Nearly 15 percent of patients in the placebo group experienced fractures, while only 5 percent of the patients in the treatment group experienced fractures, at 12 months.¹⁶ A reduction of 70 percent in fractures of the vertebrae, as compared to placebo, was calculated for both risedronate groups. Significance was found overall in the lumbar spine, femoral neck and femoral trochanter in both the 2.5 mg and 5 mg treatment groups ($p < 0.001$, $p < 0.004$, $p < 0.010$, respectively). Also, reported adverse events were similar among treat-

ment and placebo groups. The treatment groups receiving 5 mg risedronate reported a higher incidence of back pain and arthralgia when compared to placebo. However, these side effects, along with other GI symptoms such as abdominal pain and gastritis, were mild and not considered relevant. Gastrointestinal side effects were reported but were similar among treatment and placebo groups; none being reported as severe.

Overall, Reid and colleagues showed that in patients on high doses of long-term glucocorticoid therapy, 5 mg of risedronate significantly increases BMD while dosing of 2.5 mg is less effective.¹⁶ Additionally, fractures were reduced in the treatment groups as compared to the placebo group. There was a significant increase (3 percent) in BMD of the lumbar spine after 12 months of therapy with 5 mg risedronate, in addition to a significant increase in BMD of the trochanter and femoral neck. Risedronate was also well tolerated in the study and can be recommended in the studied patient population.

Zoledronic Acid (Reclast®) Parenteral Therapy

Zoledronic acid is a bisphosphonate that is unique in its administration and frequency. It targets farnesyl pyrophosphate synthase in osteoclasts located in areas of high bone turnover.¹⁷ The drug only needs to be administered intravenously once a year because of its high affinity for mineralized bone. This schedule is appealing for prescribers with patients that have compliance issues.

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) group performed a year long, randomized, double-blind, double-dummy, noninferiority study comparing zoledronic acid with risedronate.¹⁸ Both genders aged 18 to 85 years could participate in the study. The main goal of the study was to prove that zoledronic acid 5 mg intravenously is noninferior to oral risedronate 5 mg daily when looking at percentage change from baseline in BMD of the lumbar spine (primary outcome), total hip, femoral neck, trochanter and distal radius (secondary outcomes) after 12 months. Bone turnover markers and adverse events were also compared and assessed. All patients in the study were required to take vitamin D and calcium before the trial began and throughout the trial. The groups were randomized in a one to one ratio into either the zoledronic acid group or the risedronate group and also into either a treatment or prevention group based on the initiation of glucocorticoid therapy (less than three months was considered prevention and greater than three months was considered treatment). The trial confirmed that zoledronic acid is noninferior to risedronate in the treatment and prevention of GIO. The HORIZON group concluded that after 12 months zoledronic acid increased lumbar spine BMD in prevention and treatment when assessed at all test areas of the body with the exception of the prevention of GIO of the distal radius. Perhaps more importantly, when the BMD of the lumbar spine was tested at six months it was significantly higher than the risedronate group. This is significant because patients can start to see GIO within a few months of glucocorticoid thera-

py. Therefore, the faster a drug can begin showing considerable effects of GIO prevention or treatment, the better.

In the HORIZON study, zoledronic acid did have significantly higher occurrence of adverse events as compared to risedronate.¹⁸ The study found within the first three days after the infusion of zoledronic acid, flu-like illnesses and pyrexia were reported; however, after that time period elapsed, reporting of adverse events was similar between the groups. A review article discussing the management of common adverse events associated with intravenous bisphosphonates found flu-like illnesses to be frequently reported but transient in duration.¹⁹ The most severe adverse event reported for both groups was worsening of rheumatoid arthritis, and the main difference was seen in the higher reporting of pyrexia in the patients receiving zoledronic acid.¹⁸ The administration of acetaminophen immediately following the infusion of zoledronic acid is suggested to reduce frequency or duration of pyrexia, myalgia, arthralgia and headache within the first three days.¹⁷

The HORIZON study convinced the American College of Rheumatology to include zoledronic acid in their 2010 recommendations for the prevention and treatment of GIO.¹⁰ The recommendations according to FRAX score can be found in Table 1. Because the FRAX score can only be used in postmenopausal patients or men over 50 years of age, there are also recommendations for premenopausal women and men less than 50 years of age that have a history of fragility fracture. Zoledronic acid is recommended if taking at least 7.5 mg of prednisone for one to three months and of nonchildbearing potential. If at least three months of glucocorticoid therapy are expected for those with a history of fragility fractures and of nonchildbearing potential, zoledronic acid is a recommendation for any dose. Zoledronic acid is not recommended for women of childbearing potential. All of the recommendations provided were level B evidence, meaning that the data came from a single, randomized, controlled trial or nonrandomized study.

The absolute contraindications for zoledronic acid therapy include hypocalcemia (unless adequately treated), a creatinine clearance less than 35 mL/min or evidence of acute renal impairment, pregnancy, and hypersensitivity to any component in zoledronic acid.¹⁷ Patient warnings include osteonecrosis of the jaw, atypical femoral fractures, musculoskeletal pain and bronchoconstriction in aspirin-sensitive patients. While these are very rare side effects, patients should receive appropriate education about these possible occurrences and what to do if they occur. Zoledronic acid should be considered in patients that have compliance problems and could be considered a first-line option for many patients as evidenced by a survey at the end of the HORIZON study.¹⁸ The survey asked patients to comment on their preferences of route of administration regarding convenience, satisfaction and willingness to use long term. Most patients reported in the survey that they favored the intravenous preparation over the oral for convenience and satisfaction and stated they were willing to take the intravenous preparation.

Teriparatide

Glucocorticoid therapy induces bone loss by inhibiting osteoblast formation and activating osteoblast apoptosis.²⁰ Teriparatide is a recombinant human parathyroid hormone (PTH), which is a newer therapy for the treatment of GIO, and replaces older therapies such as testosterone and estrogen.¹⁰ The administration of teriparatide once daily induces bone formation, which allows for an increase in bone mass thus reducing the risk of vertebral and nonvertebral fractures.²⁰

Please refer to Table 1 for the American College of Rheumatology's guidelines for recommendations of the therapeutic usage of teriparatide based on FRAX score and glucocorticoid therapy.¹⁰ Similar to the previously mentioned medications, patient monitoring is recommended during usage. In addition to the recommendations above, for premenopausal women who have childbearing potential along with a fragility fracture, teriparatide is recommended if the patient is on glucocorticoids (dose of 7.5 mg or more of prednisone) for more than three months. For men below 50 years of age, teriparatide is recommended if glucocorticoid usage is longer than three months and if a fragility fracture exists. Currently, the use of teriparatide therapy for GIO is only approved for at most 24 months of therapy.²¹

The effectiveness of the teriparatide was studied in a randomized, double-blind, controlled trial conducted by Saag and colleagues.²⁰ Teriparatide was compared with alendronate in 428 females and males who were diagnosed with established glucocorticoid-induced osteoporosis. These patients were defined as patients diagnosed with osteoporosis and were on a glucocorticoid therapy for at least three months.

Two hundred fourteen patients were randomly assigned to either receive 20 mcg of subcutaneous injectable teriparatide once daily with an oral placebo or 10 mg of alendronate once daily orally with an injectable placebo. Patients also received 1000 mg calcium carbonate and vitamin D daily. There were no significant differences between the patients in the two study groups when baseline characteristics were accounted. The study was conducted for 18 months. The main focus of the study was to measure the change in BMD of the lumbar spine from baseline to 18 months. Additional outcomes assessed included changes in BMD at the total hip, markers of bone turnover, and the time to fluctuations in BMD, occurrence of fractures, and safety.

It was found that the mean BMD in the lumbar spine improved more in the teriparatide group than in the alendronate group (teriparatide: 7.2 ± 0.7 percent and alendronate: 3.4 ± 0.7 percent, $P < 0.001$). There was a significant difference ($P < 0.001$) between the groups six months into the study. At 18 months, the measured difference from baseline for teriparatide was 3.8 ± 0.6 percent but only 2.4 ± 0.6 percent for alendronate. When analyzing markers of bone turnover, N-terminal propeptide of type I collagen served as an indicator of bone formation. C-telopeptide of type I collagen

served as an indicator of resorption. Both of these markers increased 69.8 percent and 44.8 percent measuring from baseline, respectively. Alendronate showed a decrease in markers followed by constant suppressed levels. The teriparatide group also had fewer new vertebral fractures than in the alendronate group showing a 0.6 percent occurrence in the teriparatide group and 6.1 percent occurrence in the alendronate group while $P = 0.004$. It was shown that there were more nonvertebral fractures for patients who received teriparatide. However, the occurrence of nonvertebral fractures did not show a big difference with 5.6 percent occurrence in the teriparatide group versus 3.7 percent in the alendronate group with $P=0.36$.

Osteoporosis patients have a lowered ability to convert 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxyvitamin D [1,25(OH)₂D], which is the active form.²² Cosman and colleagues found that with doses greater than 7.5 mg per day, teriparatide increased renal activity in order to promote the conversion of vitamin D. The increased vitamin D conversion to its active form allows for an increased calcium absorption in the GI tract, renal conservation of calcium, skeletal calcium release and increase in serum calcium concentrations. This is supported by the study conducted by Saag and colleagues which showed that, similar to the 18 month study, the 36 month study showed teriparatide patients with elevated serum calcium levels 21 percent compared to only 7 percent in alendronate patients.²³

Adverse events of teriparatide use reported include nausea, insomnia, pharyngitis, viral infection, headache, dizziness and injection site reactions.²⁰ Three patients experienced hyperuricemia and one patient experienced gout in the teriparatide group, but these adverse events did not occur in the alendronate group.

Patients with osteoporosis and elevated risk for fracture showed more improvement in BMD while receiving teriparatide when compared to patients who received alendronate.²⁰ Since BMD increased more with the usage of teriparatide therapy in GIO, it is associated with a higher volumetric BMD than alendronate.

Although teriparatide use should not exceed 24 months, a 36 month follow-up study by Saag and colleagues was conducted and found that patients treated with teriparatide showed greater increases in BMD of the lumbar spine (11 percent versus 5.3 percent) and fewer new vertebral fractures than subjects treated with alendronate.²³

Calcium and Vitamin D

Clinicians have often struggled to find the correct place for calcium and vitamin D in the treatment of osteoporosis. A double-blind, parallel-group study, performed by Sambrook and colleagues, randomized patients on corticosteroids into three groups: group 1 took calcitriol, salmon calcitonin nasal spray, and elemental calcium; group 2 took the same but had a placebo nasal spray; group 3 took calcium and placebos of the calcitriol and calcitonin.²⁴ The study looked at the effects

of the therapies on BMD while on corticosteroids. They found that calcium plus calcitriol, with or without calcitonin, prevented bone loss from the lumbar spine. The study also looked at the femoral neck and the distal radius, but none of the treatment groups prevented bone loss in these locations.

Sambrook and colleagues also did a later study that was randomized and open label.²⁵ This study compared calcitriol, vitamin D (ergocalciferol) plus calcium and alendronate plus calcium. Bone mineral density of the lumbar spine was measured every six months from baseline for two years, and femoral neck and total body were also measured as secondary end points of the study. Results from the study indicated that alendronate plus calcium was superior to the other treatments in the study. This was especially noticeable in the initial bone loss phase.

Because drugs that work more efficaciously in the prevention and treatment of GIO are now considered first-line, calcium and vitamin D are usually seen as adjunctive therapy.¹⁰ In studies that deal with the treatment of GIO, most often the patients in the treatment groups are also receiving some type of calcium and vitamin D supplementation.^{12,18}

Prevention of GIO

All patients on glucocorticoids should engage in weight-bearing exercise like running or lifting to stimulate bone remodeling.¹⁰ Regardless of the strength or duration of glucocorticoid therapy, patients should receive 1200 to 1500 mg/day of calcium (diet or supplement) in addition to 800 to 1000 IU/day of vitamin D. All of the aforementioned drugs can be initiated with the start of glucocorticoid therapy as either prevention or treatment. See Table 2 for dosage recommendations.

The Pharmacist's Role

It is estimated that more than 1 million people in the United States alone are on long-term glucocorticoid therapy.²⁶ This type of therapy elevates patients to a higher risk of osteoporosis and fractures. Most of the adverse events of the glucocorticoids occur during the first six months of therapy.

Patients on long-term glucocorticoid therapy require education and monitoring.²⁶ Pharmacists are readily available to help counsel these patients as they have the most knowledge about medications. These two factors make pharmacists, especially community pharmacists, prime candidates to assist patients who have or are at risk for GIO. Through counseling and education, pharmacists can increase patient awareness of potential risks of long-term use of glucocorticoids.²⁷ They can inform patients that cigarette smoking, excessive alcohol intake, an inactive lifestyle and hypogonadism can increase their risk for developing GIO.

McDonough and colleagues conducted a randomized control design where 15 community pharmacies were randomized to either the control group (which provided usual patient care) or the treatment group (which provided patients with education about the risks of GIO).²⁷ The treatment group re-

Table 2: Dosing for Prevention of Glucocorticoid-Induced Osteoporosis.^{9,10,14,17}

Drug	Route	Dose	Frequency
Alendronate	Oral	5 mg / 35 mg	Daily/Weekly
Risedronate	Oral	5 mg / 35 mg	Daily/Weekly
Zoledronic Acid	Intravenous	5 mg	Annually
Teriparatide	Subcutaneous	20 mcg	Daily

ceived education via pamphlets. The pharmacists monitored patient drug therapies and looked for potential drug-related issues. Osteoporosis risk factors were then collected through patient surveys after nine months. Variables such as using calcium supplements, discussion of GIO risk, discussion of bone density tests, reported inactivity and reported low calcium diets were compared between the two groups. There was only a significant difference between the two groups when the frequency of patients taking a calcium supplement was analyzed: control group (-6.9 percent) and the treatment group (17.1 percent) with $P < 0.05$. This study shows that community pharmacists are able to increase vitamin supplementation for patients on glucocorticoid therapy.

Additionally, pharmacists can help identify high-risk patients before glucocorticoid therapy starts and, as a result, educate patients about their risk for GIO, recommend a BMD test and potentially collaborate with a physician to initiate therapy to prevent GIO occurrence.^{26,28} It is recommended that patients start therapy on the lowest dose of glucocorticoids for the shortest length of therapy to minimize GIO risk. Patients beginning glucocorticoid therapy that will last longer than three months should be advised to have the following tests: fall risk assessment, baseline dual x-ray absorptiometry, serum 25-hydroxyvitamin D level, baseline height, assessment of prevalent fragility fractures and radiographic imaging of spine or vertebra.¹⁰ Patients should also consider appropriate lifestyle changes such as weight-bearing activities and exercise, fall prevention, smoking cessation and avoidance of excessive alcohol consumption (> two drinks/day). Furthermore, pharmacists should counsel patients on medication usage, calcium and vitamin D supplementation and the importance of adherence.^{10,28}

For patients who have been taking glucocorticoids for longer than three months, pharmacists should advise patients to consult their doctors about periodically receiving serial bone mineral density testing, assessments for incident fragility fracture, osteoporosis medication compliance, annual serum 25-hydroxyvitamin D measurements and height measurements to monitor for GIO.¹⁰

When reviewing patient profiles, pharmacists should be alert for red flags in regard to glucocorticoid therapy and GIO.²⁷ They should watch for medications that may interact with glucocorticoids such as thyroid hormone supplements and anticonvulsants. Additionally, pharmacists should check profiles or ask patients on glucocorticoids if they are also taking recommended calcium and vitamin D supplementation.

Also, pharmacists can determine when a drug holiday is necessary by analyzing therapy duration of past therapy and patient risk factors. A drug holiday is a break in therapy designed to reduce the risks of long-term glucocorticoid treatment.²⁶ Patients on drug holiday should be monitored; presenting an ideal role for the pharmacist. If the BMD decreases significantly, or if occurrence of fractures takes place, therapy should resume. If a patient is on an osteoporosis treatment holiday, the pharmacist can create an action plan and follow up with the patient every one to two years. Pharmacists can also reassess a patient's risk of fracture by utilizing FRAX to help identify when it would be appropriate to start or end a drug holiday.

Pharmacists can prevent and treat GIO via monitoring, educating patients on lifestyle and diet alterations, and providing therapeutic management.²⁶ Community pharmacists readily interact with physicians, allowing for initiation of a management process to reduce GIO. Utilizing these methods will allow for better therapeutic outcomes with interprofessional work between the pharmacist and physician along with communication with patient.

Conclusion

Osteoporosis is characterized by the presentation of low bone density influenced by individualized factors. The disease has also been shown to occur in the vast majority of patients on long-term glucocorticoid therapy. The development of GIO poses negative effects on the patient by hindering their ability to complete daily activities and lowering their quality of life through the increased risk of fracture in areas such as the hip, vertebrae and wrist. Prevention of GIO by utilizing nonpharmacologic measures such as weight-bearing

exercises like running or lifting to stimulate bone remodeling is recommended with any glucocorticoid therapy.

The same medications used for prevention are also used for treatment of GIO. Medication therapy options most frequently recommended to treat GIO consist of bisphosphonates, including alendronate oral therapy, risedronate oral therapy or zoledronic acid parenteral therapy. The most recent addition to the guidelines is teriparatide, a subcutaneous injectable therapy. Recommendations are made based on the patient's FRAX score and glucocorticoid treatment plan and are individualized to best fit the patient's lifestyle. The concurrent use of supplements such as calcium and vitamin D is beneficial to help build up BMD. Both supplements have been found to significantly improve BMD and lower fracture risk in patients.

Although therapeutic outcomes depend on patient compliance, the pharmacist can play an important role in glucocorticoid therapy. Pharmacists should counsel and assess the appropriateness of each medication to prevent GIO. After therapy is initiated, pharmacists should be involved in monitoring the wellness of the patient and evaluating if additional therapy is necessary.

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Assessment Questions

- JD, a 65 year old female, is receiving prednisone 15 mg daily as maintenance therapy for autoimmune hepatitis. JD's FRAX score indicates she is at high risk for (glucocorticoid-induced) osteoporosis. Which of the following would be appropriate therapy for JD?
 - Alendronate therapy.
 - Discontinuation of maintenance prednisone.
 - Calcium and vitamin D supplementation only.
 - No pharmacologic intervention is necessary at this time.
- Patients taking glucocorticoid therapy for at least _____ have a significant increase in developing osteoporosis.
 - 1-2 months
 - 4-8 months
 - 3-6 months
 - 1 year
- The pathophysiology of osteoporosis involves:
 - Hormones
 - Osteoclasts
 - Osteoblasts
 - All of the above
- What dose of risedronate has been shown to significantly increase bone mineral density in patients with GIO?
 - 2 mg
 - 5 mg
 - 7.5 mg
 - 12.5 mg
- JL's doctor has identified him as a high-risk patient that needs to be started on therapy to prevent glucocorticoid-induced osteoporosis. His doctor knows that JL frequently misses appointments and never calls regarding refills for his hypertension medication. Which medication would you suggest for JL?
 - Alendronate
 - Zoledronic Acid
 - Risedronate
 - Calcium alone will show benefit.
- The 2010 American College of Rheumatology guidelines recommend _____ of calcium and _____ of vitamin D.
 - 1200-1500 mg/day; 800-1000 IU/day
 - 800-1000 IU/day; 1200-1500 mg/day
 - 2200-2500 mg/day; 80-100 IU/day
 - 80-100 IU/day; 2200-2500 mg/day
- Which of the following is a contraindication to zoledronic acid therapy?
 - Untreated hypocalcemia
 - CrCl < 35 mL/min
 - Pregnancy
 - All of the above are contraindications to zoledronic acid therapy.
- What does teriparatide stimulate?
 - Osteoblast apoptosis
 - Osteoclasts
 - Osteoblastogenesis
 - Glucocorticoid-induced Osteoporosis
- What is the usual dose of teriparatide for GIO patients?
 - Oral: 20 mg once daily
 - Sublingual: 200 mcg once daily
 - SubQ: 20 mcg once daily
 - IM: 20 mcg once daily
- Pharmacists should counsel on _____ and _____ supplementation when a patient starts a glucocorticoid therapy for a duration longer than three months.
 - fish oil; St. John's Wort
 - vitamin C; calcium
 - vitamin A; vitamin C
 - vitamin D; vitamin A



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