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Intravenous Zoledronic Acid: What Are the Indications for Male Osteoporosis?

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Abstract Osteoporosis and fractures are under-recognized and undertreated, both in men and women worldwide. Male osteoporosis is not the epidemic problem that female osteoporosis is; however, the National Osteoporosis Foundation estimates that over 14 million American men have osteoporosis or low bone mass, and approximately 25% to 30% of all hip fractures occur in male individuals who incur greater morbidity and mortality than their female counterparts. Until recently, alendronate, risedronate, and teriparatide were the only pharmacologic agents approved by the US Food and Drug Administration for treating male osteoporosis. In December 2008, zoledronic acid was approved for "treatment to increase bone mass in men with osteoporosis." In 2009, zoledronic acid was also approved for "treatment and prevention of glucocorticoid-induced osteoporosis in patients (both men and women) expected to be on glucocorticoids for at least 12 months."

Keywords Osteoporosis · Bone density · Zoledronic acid · Bisphosphonate

Introduction

Osteoporosis is currently defined as "a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [1, 2]. This definition emphasizes the fact that in addition to bone density, factors contributing to bone quality (eg, bone turnover, geometry, microarchitecture) are also important determinants of the risk of fracture in men and women.

Declining bone density and bone quality with aging and other disease states lead to increasing fracture risk. Epidemiologic studies suggest that up to 2 million men have osteoporosis and another 12 million have low bone mass at risk for fractures [3]. Caucasian men have the greatest prevalence at 7%, compared with African American (5%) and Hispanic individuals (3%). The lifetime risk of osteoporotic fracture after 50 years of age for men is 25% to 30%, compared with 50% for women [4]. The prevalence of vertebral deformities in men increases gradually and is about 30% by 80 years of age [5]. The incidence of hip fractures begins to rise at an older age than vertebral fractures, increasing fivefold between the ages of 70 and 85 years [6].

The lifetime risk of hip fracture (the most important fracture in terms of morbidity, mortality, and cost [7]) is approximately 16% for Caucasian women and 6% for Caucasian men [8]. Approximately 30% of all hip fractures occur in men, and the number of male hip fractures in 30 years will approximate the epidemic number of female hip fractures today [6]. The mortality in men following hip fracture is approximately double that of women [9, 10], and higher than for age-matched patients without hip fracture.

Risk Factors for Male Osteoporosis

Risk factors for low bone density in men are well established and include genetics, hypogonadism, and glucocorticoid use [11•, 12]. It is estimated that 50% of men have some underlying secondary cause, about 30% being due to hypogonadism and 15% due to glucocorticoids.

There are firm epidemiologic studies in men (not just extrapolations from studies of women) demonstrating that

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low bone density, low body mass index (BMI <22 kg/m^2), hypogonadism, and gait and visual disturbances are all independent risk factors for fragility fractures [13–15].

As with women, the greatest risks for future fracture are low bone density, age, and the presence of a prior fracture. All are independent risk factors predicting subsequent fractures, and combining these risk factors has an additive influence on fracture risk. The risk of hip fracture doubles, and that of vertebral fractures increases fivefold, in patients with prevalent vertebral fractures.

Despite the knowledge that any fracture increases the risk of future fractures, there are still men who have had hip fractures and are not placed on antiresorptive medications to prevent future fractures. Keibzac [9] reviewed records from individuals over 50 years of age who had been admitted for an atraumatic hip fracture. He found that 32% of men compared with 17% of women had died within the next 12 months (P<0.003), and that at hospital discharge less than 5% of men had been placed on antiresorptive medications compared with 27% of the women (P<0.001) At 1 to 5 years of follow-up, only 27% of the men compared with 71% of the women were on antiresorptive therapy (P< 0.001), and most of these on calcium and vitamin D alone.

The Role of Bone Density Testing in Men

Although no clearly established recommendations exist for screening men for osteoporosis, general guidelines are beginning to emerge. Orwoll [16] has proposed the following guidelines for male osteoporosis screening: 1) screening those who have had a history of a fragility fracture, particularly at the hip; 2) radiographic evidence of osteopenia; and 3) multiple risk factors for osteoporosis, including disease states and medications affecting bone metabolism. Specifically men on glucocorticoids should be considered at very high risk, and a strong consideration should be given to initiating antiresorptive therapy if baseline bone density is low. Another group of men at significant risk of fracture are those at risk for falling. Older patients with a gait disturbance, weakness of lower extremities, inability to get out of a chair unassisted, or those using a cane or walker should be considered for screening. Other individuals suitable for screening would include those with significant immobility from pulmonary or cardiac disease, those over 70 years of age who have lost height, and possibly all men over 75 years of age.

The International Society of Clinical Densitometry (ISCD) has published guidelines for bone density testing in men [17]. These include the following:

1. Patients greater than 70 years of age regardless of other osteoporosis risk factors
2. Patients with prior fragility fracture
3. Patients with conditions widely recognized to increase the risk for bone loss and fracture, (eg, hypogonadism, corticosteroid treatment, hyperparathyroidism, alcohol abuse, anticonvulsant use, and prior gastrectomy).

The 2008 National Osteoporosis Foundation (NOF) guidelines recommend testing all men 70 years of age and older with dual-energy x-ray absorptiometry (DXA) [18]. Men with significant risks factors should undergo DXA scanning of the spine and hip. Limited data exist on quantitative CT, heel ultrasound, or other peripheral densitometry techniques in men.

Treating Osteoporosis in Men

General lifestyle modifications should include weight-bearing exercises, avoidance of tobacco and alcohol, and interventions to prevent falls. All men with osteoporosis should be prescribed 1,200 mg/d of calcium and 800 to 1,000 units of vitamin D. A recent systematic review demonstrated that daily ingestion of 1,200 mg of calcium with 800 IU or more of vitamin D reduced osteoporotic fractures significantly in men and women 50 years of age or older [19].

Testosterone Replacement

Testosterone deficiency is a major cause of osteoporosis in men, accounting for 30% of cases [20]. Testosterone replacement has been shown to decrease bone loss in hypogonadal men; however, long-term studies in men with osteoporosis have been limited. There is currently inadequate data to recommend testosterone replacement for treating osteoporosis and preventing fractures. From a practical standpoint, there are often relative or absolute contraindications to testosterone replacement (eg, occult or evident prostate cancer, benign prostatic hypertrophy, congestive heart failure). Finally, studies of alendronate [21] and recombinant parathyroid hormone (rPTH) [22] in men with osteoporosis demonstrate that bone mineral density (BMD) increases to a similar extent regardless of baseline gonadal status (free testosterone level). Therefore, there would be no need to combine testosterone with alendronate or rPTH for the sole purpose of treating osteoporosis even if the male patient is hypogonadal.

Alendronate, Risedronate, and rPTH

Alendronate was the first agent to be approved by the US Food and Drug Administration (FDA) in men, based upon a 24-month trial of 241 men treated with 10 mg of alendronate daily versus placebo [21]. Approximately two thirds of the men were eugonadal and one third were hypogonadal. Alendronate significantly increased bone

density in the hip and spine compared with placebo. The study was not powered to assess reductions in fractures.

Boonen et al. [23] randomized 284 men with osteoporosis to weekly risedronate, 35 mg, or placebo in a 2:1 ratio and demonstrated significant increases in bone density at the hip and spine in those men taking risedronate compared with placebo. There was a trend to reduction in fractures but this was not significant because this study also was not powered for fracture reduction.

Teriparatide is approved in the United States for treating osteoporosis in men considered at high risk for fracture. Orwoll et al. [22] demonstrated that daily administration of 20 μg of teriparatide significantly increased bone density at the hip and spine compared with placebo in eugonadal and hypogonadal men with osteoporosis.

Zoledronic Acid

Zoledronic acid is indicated by the US FDA for treating osteoporosis in postmenopausal women, preventing osteoporosis in postmenopausal women, treating and preventing glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months, and treating to increase bone mass in men with osteoporosis [24].

Zoledronic acid, a third-generation bisphosphonate, is the monohydrate of 1-hydroxy-2 ([H-imidazol-1-yl] ethylidene) bisphosphonic acid. Zoledronic acid has two nitrogen atoms, contained in a heterocyclic imidazole ring. Nitrogen-containing bisphosphonates exert their cellular effects by inhibiting farnesyl diphosphate synthase (FPP). Zoledronic acid has been shown to be the most potent inhibitor of FPP to date [25]. In addition, because it is administered as a once-yearly infusion, zoledronic acid ensures bisphosphonate adherence and persistence over the entire 12-month dosing interval and bypasses the gastrointestinal (GI) absorption and potential upper GI irritation problems associated with oral bisphosphonates.

Osteoporosis Trials

The HORIZON-PFT

As is the case with most pharmacologic agents used for osteoporosis, the first pivotal trials are usually performed in women because the disease is more prevalent in this gender.

Zoledronic acid was approved by the FDA for treating postmenopausal osteoporosis based on the pivotal HORIZON PFT [26••], a 3-year, randomized, double-blind, placebo-controlled clinical trial involving 7,736 women from 240 clinical centers in 27 countries. This study was designed to evaluate the potential of once-yearly zoledronic acid, 5 mg, to decrease fracture risk in postmenopausal women with osteoporosis. The study included women 65 to 89 years of age with a femoral neck T-score of −2.5 or less, or of −1.5 or less with one moderate or two mild prevalent vertebral fractures. Subjects were stratified into two groups: those not receiving other current osteoporosis therapy (stratum I; 79% of the cohort) and those concurrently receiving selective estrogen receptor modulators, calcitonin, hormone therapy/estrogen therapy, or tibolone (stratum II; 21% of the cohort). Patients received an annual infusion of zoledronic acid, 5 mg, or placebo, and all patients received supplements of calcium, 1,000 to 1,500 mg/d, and vitamin D, 400 to 1,200 IU/d.

At the end of 3 years of follow-up, there were statistically significant decreases for the zoledronic acid group compared with placebo in the relative risk of morphometric vertebral fractures (70%), clinical vertebral fractures (77%), hip fractures (41%), and nonvertebral fractures (25%). Lumbar spine and total hip BMD were significantly increased (6.7 % and 6.0%, respectively) versus placebo. Mean serum C-telopeptide and bone-specific alkaline phosphatase levels were reduced to within the normal premenopausal range.

The HORIZON-RFT

The next major trial with zoledronic acid, and one that included men, was the HORIZON-RFT [27], an international, multicenter, randomized, double-blind, placebo-controlled trial involving patients with recent low-trauma hip fracture. All patients enrolled in the trial (508 men, 1,619 women) had undergone repair of a hip fracture within 90 days of the initial study treatment infusion. Patients were randomly assigned to receive an intravenous infusion of 5 mg of zoledronic acid or placebo every 12 months for the study duration. If the serum 25-hydroxyvitamin D level was 15 ng/mL or less or if the level was not available, patients received a loading dose of vitamin D_3 or vitamin D_2 (at a dose of 50,000–125,000 IU given orally or intramuscularly) at least 14 days before the first treatment infusion. Thereafter, all patients received daily supplementation with oral calcium (1,000–1,500 mg) and vitamin D (800–1,200 IU). The median follow-up was 1.9 years. The study was an event-driven trial and the primary end point was a new clinical fracture.

The rates of any new clinical fracture were 8.6% in the zoledronic acid group versus 13.9% in the placebo group, a 35% risk reduction with zoledronic acid (P=0.001); the corresponding rates of new clinical vertebral fractures were 1.7% versus 3.8%, a risk reduction of 46% (P=0.02). A total of 101 of 1,054 patients in the zoledronic acid group (9.6%) and 141 of 1,057 patients in the placebo group (13.3%) died from any cause. There was a greater mortality benefit for men (absolute risk reduction, 6.4%) than for women (2.8%), with a marked reduction in cardiac-related deaths (incidence, 2.9% for men, and 7.7% for women). No

adverse effects of zoledronic acid on the healing of fractures were noted.

The HORIZON-Male Osteoporosis Trial

Intravenous zoledronic acid has also been shown to increase BMD in men with osteoporosis or significant osteoporosis secondary to hypogonadism [24]. A randomized, multicenter, double-blind, active-controlled trial compared BMD results for intravenous zoledronic acid, 5 mg, once yearly (n=154) and oral alendronate, 70 mg/wk (n=148), over 2 years. All subjects received 1,000 mg of oral calcium plus 800 to 1,000 IU of vitamin D supplementation per day. This was a noninferiority trial whose primary end point was percentage change in lumbar spine BMD relative to baseline. Zoledronic acid increased lumbar spine BMD at month 24 by 6% relative to baseline, which was comparable to alendronate.

The HORIZON-GIO Trial

Intravenous zoledronic acid, 5 mg, has also been shown to be effective in treating and preventing glucocorticoid-induced osteoporosis (GIO) in men and women [28] in a 1-year randomized, double-blind, active-controlled study of 833 men and women treated with ≥7.5 mg/d of oral prednisone. Patients were stratified into the prevention and treatment groups according to the duration of corticosteroid use at study entry (≤3 months and >3 months, respectively). In the prevention group, there were 88 men (31%) and 200 women (69%). In the treatment group, there were 177 men (32%) and 368 women (68%). Patients received a single 5-mg zoledronic acid infusion or 5-mg oral risedronate per day for 12 months. All patients received 1,000 mg of calcium plus 400 to 1,000 IU of vitamin D. The primary end point was percentage change from baseline in lumbar spine BMD. Zoledronic acid produced significantly greater increases in lumbar spine BMD compared with risedronate in both the treatment and prevention subpopulations at 12 months (treatment subpopulation: zoledronic acid, 4.1% vs risedronate, 2.7%; P<0.001; prevention subpopulation: zoledronic acid, 2.6% vs risedronate, 0.6%; P<0.001). Although this trial was designed to demonstrate that the percentage change in lumbar spine BMD at 12 months with zoledronic acid was noninferior to risedronate, the increases in spine BMD at 12 months seen with zoledronic acid were significantly greater than risedronate for men (P<0.05) and women (P< 0.01) for both treatment and prevention subpopulations.

Safety and Tolerability of Zoledronic Acid

The most common adverse events with zoledronic acid are transient post-dose flu-like symptoms. The occurrence of such symptoms is common to the class of intravenous nitrogen-containing bisphosphonates, especially in patients who are bisphosphonate-naïve. In the zoledronic acid HORIZON-PFT, fever and myalgia were reported in 16% and 9%, respectively, of zoledronic acid–treated patients during the first 3 days following administration [26••]. In general, these symptoms resolve within 3 days and can be effectively managed with acetaminophen [27]. Post-dose symptoms also tend to be reduced with administration of subsequent doses of the drug. In a trial of patients given zoledronic acid who were previously treated with alendronate, the frequency of post-dose symptoms in patients who switched directly from alendronate to zoledronic acid was low [29].

Bisphosphonates should not be given to patients with significant renal impairment. In the HORIZON-PFT, which included more than 7,700 patients, changes in calculated creatinine clearance over 3 years were similar to those seen with placebo [26••]. Small, transient elevations in serum creatinine were reported within 10 days of dosing in 1.8% of the zoledronic acid group versus 0.8% of placebo patients; however, these elevations resolved without specific therapy, and all of these patients were subsequently redosed at the next scheduled infusion. In the HORIZON-RFT, which included 2,100 patients, there were no differences between the zoledronic acid and the placebo groups with respect to long-term renal function [27]. As with other bisphosphonates, zoledronic acid should not be used in patients with a creatinine clearance of less than 35 mL/min. Patients should be adequately hydrated before infusion, and the infusion time should not be less than 15 min.

Hypocalcemia may occur following zoledronic acid infusion and may, in rare instances, be symptomatic. Hypocalcemia (defined as declines of serum calcium levels to <7.5 mg/dL) was reported in 0.2% of patients taking zoledronic acid in the HORIZON-PFT [26••]; all cases were transient and asymptomatic. In the HORIZON-RFT [27], following pretreatment with vitamin D, no patients had serum calcium levels less than 7.5 mg/dL. In patients considered candidates for zoledronic acid, risk factors for hypocalcemia (including vitamin D deficiency, calcium or vitamin D malabsorption, and parathyroid gland insufficiency [due to prior thyroid surgery or irradiation]) should be evaluated. A normal serum calcium level should be obtained before infusion.

The overall incidence of atrial fibrillation adverse events was similar in the zoledronic acid and placebo groups in the HORIZON-PFT, RFT, Male Osteoporosis, and GIO trials. An unexplained imbalance in the rate of atrial fibrillation serious adverse events was reported for the zoledronic acid group in the HORIZON-PFT (1.3% vs 0.5% in placebo-treated patients) [26••]. The timing of these events did not correspond with administration of zoledronic acid infusions

or post-infusion alterations in serum electrolytes. In the HORIZON-RFT, the incidence of atrial fibrillation serious adverse events was 1.0% in patients taking zoledronic acid versus 1.2% in patients taking placebo [27].

Osteonecrosis of the jaw (ONJ) is a rare disorder characterized by nonhealing exposed bone in the maxillofacial region (spontaneous or induced by oral surgery) despite proper medical care, lasting for at least 8 weeks [30]. ONJ is often associated with infection of the soft tissue and/or bone. Most cases have been in cancer patients (breast cancer and multiple myeloma patients) receiving monthly intravenous bisphosphonates. Other risk factors for ONJ include malnutrition, local radiation, concurrent glucocorticoids, and systemic chemotherapy. In more than 7,700 patients in the HORIZON-PFT (N=7,735), no spontaneous cases of ONJ were reported [29]. A thorough search of the trial database for any events involving the oral cavity identified one potential case in the placebo group and the zoledronic acid group. Both cases resolved with antibiotic therapy and limited debridement. No cases of ONJ were reported in the HORIZON-RFT, Male Osteoporosis, or GIO trials.

In the HORIZON-Male Osteoporosis and GIO trials, adverse events occurred more frequently in the intravenous zoledronic acid–treated versus the active control group during the first 3 days after infusion, largely due to transient post-dose symptoms. The overall incidence of adverse events was otherwise similar.

Conclusions

Osteoporosis in men is still an under-recognized and undertreated disorder. Risk factors for low bone density in men (predominantly glucocorticoid use and hypogonadism) are now well established, and guidelines (ISCD and NOF) now exist for when to test men for low bone density, even before fractures.

Zoledronic acid is a first-line treatment for men with osteoporosis based upon studies demonstrating its efficacy and safety. There may be special groups of patients in which it is especially helpful. A number of men may not be able tolerate oral bisphosphonates due to upper GI disorders (eg, gastroesophageal reflux or dysphagia). Some, such as stroke patients, may not be able to sit upright for 30 min, a requirement necessary to avoid esophageal toxicity with oral bisphosphonates. Many elderly patients suffer from polypharmacy and/or cognitive dysfunction, which significantly complicate persistence with medication. It is now well recognized that less than 100% persistence with oral bisphosphonate leads to suboptimal fracture reduction [31]. Once-yearly dosing with zoledronic acid should lead to improved compliance and improved fracture reduction in this population by ensuring total delivery of drug.

Clinical Trial Acronyms

HORIZON-GIO—Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly-Glucocorticoid-Induced Osteoporosis Trial; HORIZON PFT—Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT—Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Recurrent Fracture Trial.

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