One Year Zoledronic Acid Therapy In Postmenopausal Osteoporosis

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Citation

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Abstract

Osteoporosis is a chronic and progressive disorder characterized by reduced bone strength and increased susceptibility to fracture by minor trauma. Numerous safe and effective treatments can reduce the risk and recurrent fractures with the use of oral bisphosphonate therapy. However, some patients experience side effects or have contraindications to oral bisphophonate therapy. In the case of such individuals, we designed an observational clinical test to assess the efficacy and safety of a 4 mg annual intravenous administration with zoledronic acid in osteoporotic women, and in preventing clinically evident fractures following low trauma. The zoledronic acid is a new generation, efficacious and well-tolerated intravenous bisphosphonate that is the most potent updated inhibitor of bone resorption.

Methods: We included a total of 20 postmenopausal women raging from 52 to 80 years old. (mean age 64.7 +-9.2 years old) , ambulatory patients unwilling or unable to use an oral bisphosphonate. Each participant had a Bone Mineral Density (BMD) measurement (Norland XR 36) in hip and spine, previous to this study and another measurement was taken at one year later. The Group receiving zoledronic acid 4 mg stat by one hour intravenous infusions.

Results: At one year the increase of the BMD, in spine, was positive in 17 patients with an average of +4.5% and was negative in 3 patients with an average of -2.46%. In trochanter area, 12 of responded positively with +4.5% and 8 patients did not respond with -4.2%. The non responding patients were older than 70 years, with a height ≤ 160 cm., weight ≤ 55 kg. and BMI ≤ 24 kg/cm2 . The adverse events were myalgias 40% (8/20), symptoms similar to influenza 10% (2/20), and all were relieved with paracetamol. There were not axial or peripheral fractures in the year following to treatment
In Conclusion, the result of this observational study evidenced that the yearly intravenous administration schedule of zoledronic acid, is safe and effective, based on change in BMD and prevented hip and spine fractures in women who have osteoporosis.

INTRODUCTION

Osteoporosis is a chronic and progressive disorder characterized by reduced bone strength and increased susceptibility to fracture to minor trauma ([11]). These fractures increases as bone density decreases and this progressive bone loss and increased risk of falling by sarcopenia are frequent with advancing age. The fractures consequence: pain, disability, deformity, and sometimes premature death, are at least some of the reconognized clinical sequelae of osteoporosis ([2]).

Numerous safe and effective treatments can reduce the risk for recurrent fractures with the use of oral bisphosphonate, a type of drugs is approved for the prevention and treatment of osteoporosis. The amino-bisphophonate Alendronate and Risedronate are currently approved and all subgroup of examined patients may obtain beneficial effects for several years. However, in some patients, such as those experiencing adverse side effect in the upper gastrointestinal or those unable to comply with treatment guidelines because they cannot tolerate oral administratation , are not able to get up from the bed, or in glucocorticoides therapy, oral bisphophonates may be contraindicated or unsuitable ([8]).

The Zoledronic acid or zoledronate is a new generation of efficacious and well-tolerated intravenous bisphosphonates, that is the most potent inhibitor of bone resorption to date([4], [6]), may also be an attractive option for the treatment of postmenopausal osteoporosis if a large ongoing trial proves that a single annual injection of this compound allows comparable effects on bone turnover, bone mineral density, and osteoporotic fracture risk reduction as compare to those seen with weekly oral dosing with bisphosphonates . Furthermore, the zoledronate could be appropriate in patients

unable to tolerate the oral bisphosphonate ([12]).

We designed an observational clinical trial testing the efficacy and safety of an annual intravenous administration with zoledronic acid in osteoporotic women, and in preventing clinically evident fractures following low trauma.

METHODS

We enrolled participants from the Merida City (Venezuela), and conducted a observational prospective trial between December 2003 to December 2004 .To determine whether zoledronic acid (ZOMETA ® NOVARTIS AG. BASEL) 4 mg. I.V. administered annually increases bone mineral density and protect against clinical fractures in postmenopausal women. The inclusion criteria were post menopausal women aged 50 years and older, ambulatory and patients unwilling or unable to use an oral bisphophonate. The exclusion criterion was cognitive impairment or delirium, renal or another serious disease. We took this base line characteristic: Age (yr), Weight (kg), Height (cm), Body Mass Index (BMI) (kg/m2). The postmenopausal women were defined as having no menstrual period during ≥ one year prior to enrollment.

Each participant had a Bone Mineral Density (BMD) measurement in hip and spine using DXA (Norland XR 36), at randomization and one year later. Local quality assurance procedure (calibrated daily and licensed technicians) be used to asses the reliability of the DXA measurement. World Health Organization criteria for osteoporosis were applied for this analysis ([16]). T score were calculated using a standard formula. Percentage change of T-score from the base line was recordered for each patient.

Every woman was informed about the treatment and gave written informed consent.

A total of 20 postmenopausal women 52 to 80 years of age (mean age 64.7±9.2 years old).In all the women naturally menopause occurred at least in the previous four years previously. We watched a weight of 58.2±10.5 kg (37-62 Kg), a height 153.2±6.8 cm (142-157 cm), and BMI 25.97±3.99 kg/cm² (19-36 Kg/cm²).

The group received zoledronic acid 4 mg STAT by intravenous infusions in 250 ml of glucose- physiologic solution over one hour period . All received a calcium supplement (1.5 gr. per day) and Vit. D (800 IU per day).

The adverse event (myalgias or flu-like illness) was treated with acetaminophen 1gr. every six hour SOS.

RESULTS

The results of this paper are shown in the table 1 and 2. The increase of the BMD, in spine, to one year was positive in 17 patients with an average of +4.5%(rank 0.0% to +12.90% p=0.014) was negative in 3 patients with –2.46% (rank-.80% to –3.10 %). In Hip 12 they responded in a positive way with +4.5% (rank from +.70% to +11.40 % p=0.33) and 8 patients with –4.2 % (rank from -.40 to –8.10 %) did not respond (Table 1). According to the age, improvement was found in spine in 92.9%% of those under 70 years old (13/14) and did not respond the 16.6% of the older than 70 years (1/6). Whereas in the hip >70 years old increased 71.4% (10/14) and the older than 70 years lose 66.7% (4/6). When analyzing the height the ≤160 cm. 87.5 %(14/16) and 56.3% (9/16)increased in spine and hip respectly , but in the group ≥ 160 cm 25%(1/4) lost in spine and 25%(1/4) in hip . In the same way, in hip, those with a weigh ≤ 55 kg 57.1% (4/7) lost and 42.9% (3/7) increased; in spine14.3% (1/7) lost and 85.7% (6/7) gain . When we related Hip and BMI there was evidence that the ≤ 24 kg/cm²; lost 71.4% (5/7) and, between 25 and 29 kg/cm², 76.9% (10/13) increased. In spine those who had ≤24 kg/cm² 42.9 % (3/7), lost DMO; between 25 and 29 kg/cm² 100% (13/13) increased DMO(Table 2). The adverse events were myalgias 40% (8/20) and flu-like illness 10% (2/20). No patient with axial or peripheral fracture in the year following to the treatment.

{image:1}

{image:2}

DISCUSSION

Oral amino-bisphophonates are currently among the most effective therapies for the treatment for postmenopausal osteoporosis. However some patients are unable to receive oral treatment. An intravenously administered bisphophonate can provide an attractive treatment option and offers plenty of a need solution to this problem.

The result of this observational study evidenced the yearly intravenous administration schedule of zoledronic acid, is safe and effective, results in changes in BMD and prevention of a hip and spine fractures in the women who had osteoporosis. A previous paper with five regimes of zoledronic acid had BMD (Hologic) increased in spine from 4.3% to 5.1% and between 3.1% to 3.5% in hip, greater than those in placebo group, at 12 month P<0.001 ([12]).In our

study the BMD (Norland XR 36) increased was 4.5% in spine as well as in hip . Both similar study to those observed with daily or weekly oral bisphophonate therapy, alendronate mean increased in spine and Total Hip at 10 years 13.7% and 6.7%,respectively ([1]) and risedronate over 5 years 9.3% in lumbar spine , femoral neck 2.2% and trochanter 5.7% ([15]).

Bone Mineral Density testing is a noninvasive measurement to diagnose osteoporosis or low bone density, predict fracture risk, and monitor changes in bone density over time([17]). In this study only the change of BMD in hip and spine one year later was chosen as the primary endpoint. The apparent loss of BMD at the total hip and spine during one year of therapy do not affect the reduction in fracture risk (no symptomatic vertebral fracture or non vertebral). The lack of predictive precision of BMD for changes in fracture risk means that the usefulness of BMD as a surrogate for efficacy in fracture risk reduction in clinical trial may be limited. While BMD measurement while still important in a clinical setting is in itself insufficient to accurately predict fracture risk or measure treatment effects of an antiosteoporotic drug. Clinical experience with patient follow-up strongly suggests that bone quality must also be taken into account bone strength reflects both bone density and bone quality. ([3], [5], [7],[10], [13], [16]).

Increased body weight has emerged in recent years as a potential modifier of osteoporosis risk and body mass index (BMI), a height-adjusted derivative of body weight, has been accorded with the same attention. The NORA study demonstrated decreased odds of osteoporosis with increasing BMI and reported BMI as a BMD- protective factor ([14]). Our study investigates the zoledronic acid positive effect on the interaction of BMI (more than 25 Kg/m²) and the increase of BMD in hip and spine.

Calcium and vitamin D supplementation are always necessary to be added to any antiosteoporotic treatment and can prevent fractures and it is possible that with supplementation of calcium(1500 mg) and vitamin D(800IU) provided to the women in this study, the effects of zoledronic acid treatment occurred in addition to any benefit attributable to the supplementation ([3], [9]).

Our study demonstrated that in osteoporotic women older than 70 years ,in twelve month, decrease the DMO (66.7% in total hip and 16.7 % in spine) but have effect in the incidence of hip and spine fractures. In the Mc Cloung et al ([9]) assay of women 80 years of age or older, risedronate had no effect on the incidence of hip fractures.

Zoledronic acid treatment was well tolerated in our study and avoided any issues related to taking tablet, for example the needs to remain upright for 30-60 minutes following oral dosing and a treatment options for women with postmenopausal osteoporosis in whom oral bisphophonate may not be the most appropriate therapy. In overall, the incidence and types of adverse events were similar to those observed in previous study. The adverse event (myalgias and flu-like symptoms) were common in patients receiving intravenous amino-bisphophonate, were transient mild to moderates and were suppressed with acetaminophen ([12]).

Zoledronic acid, a new generation of bisphophonate, has the advantage of great potency ([4], [6]) and long duration of remission and a one hour's infusion time. No symptomatic fractures vertebral or non vertebral occurred within one year after the intravenous zoledronate. No clinical sequels were seen.

The role of I.V amino-bisphophonate in osteoporosis management is still in development and continues to be studied. This trial may serve as a model for a design of large simple randomized, double-blind, placebo- controlled trial.

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