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Three Monthly Intravenous Injections of Ibandronate in the Treatment of Postmenopausal Osteoporosis

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ABSTRACT

Background: Osteoporosis is a chronic condition that generally requires long-term therapy for fracture risk reduction to become apparent. Bisphosphonates are important therapeutics in postmenopausal osteoporosis. However, they are currently associated with stringent dosing instructions that may impair patient compliance and hence therapeutic efficacy. Intravenous (IV) treatment with an aminobisphosphonate, pamidronate was effective, but required infusions. Ibandronate, a new very potent aminobisphosphonate, can be administered safely as an IV bolus injection, and therefore offers an interesting alternative suitable for outpatient treatment.

Objective: To determine the effectiveness of three monthly IV bolusIbandronate injections in terms of increase in bone mineral density at hip and spine in postmenopausal women.

Study Design: Randomized Placebo controlled study.

Place and Duration of Study: This study was conducted in Gynae "B" Unit of Khyber Teaching Hospital, Peshawar from Feb 2012 to Jan 2013

Materials and Methods: 150ambulatory Postmenopausal women 55-75 years old, and atleast 5years since menopause with osteoporosis ((bone mineral density [BMD] < −2.5 SD T score) received a placebo or IbandronateIV bolus injection(3 mg) every 3 months. All patients received 1 g calcium/day. BMD, expressed in T score, was measured by dual-energy x-ray absorptiometry (DEXA) at lumbar spine and hip. Exclusion criteria were a disease, disorder, or therapy (within the last 6 months) known to influence bone metabolism; prior treatment with oral or intravenous bisphosphonates; Baseline radiographic assessment for prevalent vertebral fractures was not performed in this study. All participants provided written informed consent.

Results: There were 150 Postmenopausal women with mean age of 62 years.Lumbar spine BMD (L2 to L4) decreased by 2.9% and hip by 3.2% in the placebo group, but increased by 5.2% at 12 months for Ibandronategroup. The increase was statistically significantly different from placebo ($P < 0.001$) group. After 1 year total hip BMD increased significantly by 4.5%.

Conclusion: Treatment of postmenopausal osteoporosis by interval IV bolus injections of the bisphosphonate Ibandronateis an effective and convenient way of increasing BMD at hip and spine. The high potency of Ibandronate allows 3-month interval bolus IV injections as a new therapeutic approach with optimal compliance.

Key Words: Postmenopausal, osteoporosis, Ibandronate, Bone mineral density

INTRODUCTION

Osteoporosis is a common chronic condition leading to a high risk of fragility fractures, which imposes a considerable and growing socioeconomic burden[1,2]. The National Osteoporosis Foundation Consensus Development Conference (NOF, 2003) defined osteoporosis as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk[1,2].

Peak bone mass in adults is achieved by age 25 to 30 years, and is largely determined by genetic factors; however, nutrition, endocrine status, physical activity, and health during growth also play a contributing role[1,3,4]. Bone loss occurs when bone resorption begins to outpace bone formation. This imbalance occurs with menopause and advancing age[1,2,3]. After menopause, women experience an accelerated bone loss of 1to 5 % per year for the first 5 to 7 years. The end result is a decrease in trabecular bone and an increased risk of fractures. It is estimated that one in three women will have an osteoporosis-related fracture during their lifetime, resulting in increased disability and mortality[1,2,3,4].

Bone mineraldensity (BMD) is a medical term referring to the amount of mineral matter per square centimeter of bones. It is used in clinical medicine as an indirect indicator of osteoporosis and fracture risk. It is measured by a procedure called densitometry[6]. The measurement is painless and non-invasive and involves low radiation exposure. Measurements are most commonly made over the lumbar spine and over the upper part of the hip. DEXA is currently the most widely used test for BMD measurement.Results are expressed as T-score[2,4]. It is the bone mineral density (BMD) at the site when compared to the young normal reference mean. It is a comparison of a patient's BMD

to that of a healthy thirty-year-old. Normal is a T-score of -1.0 or higher,osteoporosis is defined as -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman[5,6].

Bisphosphonates are highly potent inhibitors of osteoclast-mediated bone resorption both in vitro and in vivo[7]. The nitrogen-containing bisphosphonates inhibit bone resorption by various mechanisms including the acceleration of osteoclast apoptosis via inhibition of the mevalonic acid pathway and protein prenylation.[7,8]. Ibandronate is a new potent nitrogen-containing bisphosphonate that inhibits bone resorption in animal models at doses considerably lower than other bisphosphonates[8].

Bisphosphonates are poorly absorbed from the gastrointestinal (GI) tract (<1%), and the absorption is decreased further by concomitant food intake. Therefore, oral bisphosphonates should be taken with water at least 30 minutes before breakfast to achieve sufficient absorption[7,8,9]. This rigid dosing schedule is very inconvenient, particularly if patients are elderly, on concomitant medications, and/or have a busy daily schedule, and may lead to poor long-term adherence to therapy and jeopardize efficacy[10,11,12]. Because bisphosphonates are not metabolized and bind strongly for prolonged periods to areas of active bone resorption, it is conceivable that the proven efficacy with rigid daily dosing can be achieved also with an intermittent cyclical therapy[7,13,14].Ibandronate Injection, administered as a 15-30 secondsIV injection, provide an alternative for patients who have difficulty with oral bisphosphonate dosing requirements, including an inability to sit upright for 30 to 60 minutes and/or swallow a pill[14,15]. Additionally, because it will be administered by healthcare professionals, clinicians will have a greater awareness of patient compliance with therapy[15].

MATERIALS AND METHODS

This randomized placebo controlled study was conducted in Gynae "B" Unit Khyber Teaching Hospital, Peshawar from February 2011 to January 2012. Postmenopausal women were recruited (n = 150) who were aged 55-75 years, at least 5 years after menopause. BMD was measured with DEXAat the spine (L2-L4) and the hip. BMD was reported as T-score.Only those women with T score below −2.5 SD(osteoporosis) were included in the study. Women with diseases or disorders known to influence bone metabolism such as liver disease, malignant disease, primary hyperparathyroidism, active thyroid disease, Paget's disease, and osteomalacia were excluded. Additional exclusion criteria included women treated within 6 months before the study with medications known to influence the bone metabolism (corticosteroids, female sex hormones, calcitonin, and cyclosporin) as well as women previously treated with a bisphosphonate.

The women were randomized to two groups (n=75), of which one group received IVIbandronate every 3 months and the other received placebo. The purpose and benefit of the study were explained to the patients. Detailed clinical history followed by detailed physical and systemic examination was carried out. All the patients gave written informed consent before entering the study, and the study was approved by the local ethics committee and the health authorities..Ibandronate injection 3mg was given as IV bolus over 15 to 30 seconds in one of the arm vein as a 3ml vial in a prefilled syringe. Injection was givenon outpatient basis under strict aseptic condition by one of the authors.All patients were prescribed a daily dose of 400 IU of vitamin D and 1000 mg of calcium.Patients were asked to come after 3 months for a repeat dose.At the end of one year, BMD was re- measured. Percent increase in BMD at both hip and lumbar spine was calculated.

RESULTS

There were 150 postmenopausal patients out of which half (75) received Ibandronate and half (75)placebo. Mean age was 62±2 years. Mean duration since menopause was 8.3±1.5 years. Mean BMD at lumbar spine was – 3.2±0.04 T score and at hip was –2.9±0.02 T score. 72.2% of patients had BMD below -3 at lumbar spine and83.4 % of these were above 60 years.

Table No. 1: Demographic Characteristics of the study population

Parameters	Mean
Age(Years)	62±2
Time since menopause(Years)	8.3±1.5
BMD at Hip(T score)	- 3.2±0.04
BMD at Lumbar Spine(T score)	-2.9±0.02

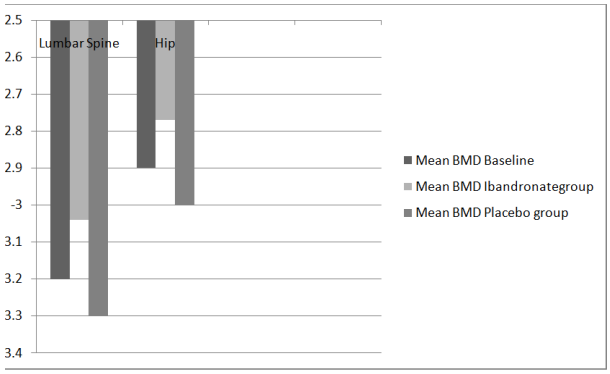

Figure No.1: Comparison of BMD between the Ibandronate group and the Placebo group before and after injectable Ibandronate therapy

In 68.3% of patients BMD at lumbar spine was less than at hip. 63.2% patients were having no symptoms despite low BMD while 28.2% were having low backache and 8.6% having generalized aches and pains. In Ibandronate group at the end of study period BMD

increased by a mean of 5.2 % at lumbar spine and by 4.5% at hip. In placebo group at lumbar spine BMD decreased by a mean of 3.2%.Thus there was statistically significant increase in the bone mineral density at lumbar spine. At hip a decrease in BMD by a mean of 2.9% was observed.

Three patients suffered hip fracture during study period and all of these belonged to placebo group while none of the patient in Ibandronate group faced this problem.

DISCUSSION

Preclinical studies with Ibandronate comparing daily and intermittent treatment regimens with the same total dose per study duration have shown equivalent results in terms of prevention of bone loss and architectural deterioration[8] In ovariectomized monkeys, intermittent therapy with Ibandronate every 30 days also indicated a dose-dependent prevention of bone loss and architectural deterioration.[16] Thus, there is evidence suggesting that a more convenient intermittent treatment schedule with Ibandronate, offering a longer therapy-free interval, would provide equivalent efficacy to daily oral dosing[17].

The goal of osteoporosis treatment is the prevention of all fracture types, including both vertebral and nonvertebral fractures. While vertebral fracture is themost common osteoporotic fracture type, nonvertebral fractures such as those of the hip can be the most debilitating and costly. Thus the global assessment of efficacy of an anti-osteoporosis treatment requires an extensive evaluation of its anti-fracture efficacy at both hip and lumbar spine. Same was done in our study.

The FDA approval of Ibandronate injection was based on results from the 1-year Dosing Intravenous Administration (DIVA) study[18,19,20]. The results of this study showed that the average increase in lumbar spine BMD at 1 year in patients treated with Ibandronate sodium injection (3 mg once every 3 months) was statistically superior to that in patients treated with the daily oral tablets (4.5 % versus 3.5 % $p< 0.001$). Our study showed an increase in BMD by 5.2 % with 3 mg IVIbandronate which is close to DIVA study.

With regard to IVIbandronate, Thiébaud and colleagues first investigated its efficacy in postmenopausal osteoporosis in a dose-ranging, randomized, placebo-controlled study of 125 women[(21)]. Results showed an increase in BMD at lumbar spine of 5.2 %. Our results at the lumber spine correlate well to this study(5.2% versus 5.2% increase in BMD). Increase in BMD at the hip however was slightly more in our study (4.5 % versus 4.2 %). This might be because of the reason that we used comparatively higher dose of Ibandronate (3mg versus 2mg).

In the IRIS study Lumbar spine BMD increased by 5.0% in the 2 mg group, and decreased by 0.04% in the placebo group[22,23]. Our Ibandronate group BMD data show remarkable similarity to this study.

Our study showed that majority of postmenopausal women(72.2%) had a very low BMD(less than -3). Most of the women belonged to a low socioeconomic class and none were taking any calcium or vitamin D supplements. They had no knowledge about osteoporosis. None of the patient was lost to followup which shows that if proper counseling is done patient do comply with the treatment offered. The convenience of less frequent dosing that is three monthly, probably played the role. None of the patient showed any serious adverse reaction to the IV treatment except for the mild flu like illness.

Postmenopausal women constitute a high risk group vulnerable to low BMD and hence increased risk of fragility fractures. Since most of our population belong to low socioeconomic strata and women in particular have decreased peak bone mass due to diet low in calcium, closely spaced pregnancies and limited exposure to sun and hence decreased vitamin D. Postmenopausal state further adds fuel to the fire with estrogen deficiency increasing the bone resorption rate.

In Pakistan so far no study has been conducted to test the efficacy of IVIbandronate. Most of the health practitioners in Pakistan prescribe oral bisphosphonates daily or weekly to postmenopausal women. This is inconvenient for the patients and they show poor compliance as often doses are missed or forgotten. Gastrointestinal side effects do occur frequently. Furthermore most of our women do prefer injectables in comparison to oral treatment due to the taboo that injectables are more effective.

BMD measurement is not done routinely in all postmenopausal women. Various studies have shown that without treatment BMD decreases by 2% to 5% per year in postmenopausal women. Same was the case in our study where the Placebo group faced a decrease in BMD by 2.9 % at lumbar spine and 3.2 % at hip. The Placebo group in IRIS study showed a decrease in BMD of only 0.06 %, but the study was conducted in western population where women have significantly more peak bone mass and greater awareness about osteoporosis.

Although DEXA is costly and not widely available but in comparison to the health benefit of its role in identifying those women at high risk of osteoporotic fractures makes it worthwhile to offer it to all postmenopausal women. Moreover it is non invasive. Once identified, measures like treatment with bisphosphonates can be offered to increase the bone mineral density and hence prevent fracturesin the long run.

CONCLUSION

Bone mineral density in postmenopausal women with osteoporosis can be increased with three monthly 3 mg

intravenous bolus injection ofIbandronate. Its efficacy coupled with its convenient dosing regimen makes it a better choice for prevention of osteoporotic fractures in postmenopausal women.

REFERENCES

1. Zafar S, Shahid Z. An overview of postmenopausal Osteoporosis. Pak J Med Sci 2004;20(3):270-6.
2. Cooper C. The crippling consequences of fractures and their impact on quality of life. Am J Med 1997;103:12.
3. Mehboob I, Warraich WH, Siddiqui AA.Who should use drugsfor osteoporosis. Pak Postgrad Med J 2001;12(3):119-21.
4. Elizabeth AK, Bess DH. Heritable and life-style determinants of bone mineral density. JBMR 1993;8:1-9.
5. Arif M, Inam M. Frequency of osteopenia and osteoporosis in different parts of North West Frontier Province. J Postgrad Med Inst 2006; 20(2):196-202.
6. Steven R, David B, Dennis MB. Clinical Use of Bone Densitometry. JAMA 2002;288(15):1889-1897
7. Roland DC, Pierre DD. Bone and mineral metabolism: Drug Insight: bisphosphonates for postmenopausal osteoporosis. Nature Reviews Endocrinol 2006;2:211-19.
8. Reginster JY, Neuprez A, Bruyere O. Ibandronate in profile: drug characteristics and clinical efficacy. Expert Opin Drug Metab Toxicol 2008;4: 941–51.
9. Mühlbauer RC, Bauss F, Schenk R, et al. A potent new bisphosphonate to inhibit bone resorption. J Bone Miner Res 1991;6:1003–11.
10. Riaz M, Abid N, Patel J, Tariq M. Knowledge about Osteoporosis among healthy women attending a tertiary care hospital. J Pak Med Assoc 2008;58(4):190-4.
11. Bauss F, Russell RG. Ibandronate in osteoporosis: preclinical data and rationale for intermittent dosing. Osteoporos Int 2004;15:423–33.
12. Weycker D, Macarios D, Edelsberg J. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporosint 2006;17:1645-52.
13. Recker R, Stakkestad JA, Chesnut CH, et al. Insufficiently dosed intravenous Ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone 2004;34:890–9.
14. Sambrook P. Quarterly intravenous injection of Ibandronate to treat osteoporosis in postmen-pausal women. Clin Interv Aging 2007; 2(1): 65–72.
15. Stakkestad JA, Benevolenskaya LI, Stepan JJ, et al. Intravenous Ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Ann Rheum Dis 2003;62:969–75.
16. Smith SY, Recker RR, Hannan M, et al. Intermittent intravenous administration of the bisphosphonate Ibandronate prevents bone loss and maintains bone strength and quality in ovariectomized cynomolgus monkeys. Bone 2003;32:45–55.
17. Christiansen C, Tanko LB, Warming L, et al. Dose dependent effects on bone resorption and formation of intermittently administered intravenous Ibandronate. Osteoporos Int 2003;14:609–13.
18. Delmas PD, Adami S, Strugala C, et al. Intravenous Ibandronate injections in postmenopausal osteoporosis: 1-year findings from the DIVA study. Arthritis Rheum 2006;54: 1838–46.
19. Eisman J, Garcia-Hernandez P, Ortiz-Luna G, et al. Intermittent intravenous Ibandronate injections are an effective treatment option in postmenopausal osteoporosis: 2-year results from DIVA Osteoporos 20061;7:212:16.
20. Lewiecki EM, Pfeilschifter J, Grant R. Continuing improvements in the efficacy of quarterly intravenous Ibandronate injection: DIVA study longterm extension. Bone 2007;S301.
21. Thiébaud D, Burckhardt P, Kriegbaum H, et al. Three monthly intravenous injections of Ibandronate in the treatment of postmenopausal osteoporosis. Am J Med 1997;103:298–307.
22. Adami S, Felsenberg D, Christiansen C, et al. Efficacy and safety of Ibandronate given by intravenous injection once every 3 months. Bone 2004; 34:881–9.
23. Silverman S, Cramer J, Sunyecz J. Women are more persistent with monthly bisphosphonate therapy compared to weekly bisphosphonates: 12 month results from two retrospective databases. J Bone Miner Res 2007;S454.

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