Zolindronic Acid in Osteoporosis- A Dexa Study

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ABSTRACT

Background: *Osteoporosis a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. We present our study analyzing the effect of Intravenous zolendronic therapy in osteoporotic individuals using the Dual Energy X-ray Absorptiometry Scan.*

Materials and method: *All patients above 50 yrs of age with osteoporosis measured by DEXA Scan of Lumbar Spine BMD (T-score<-2.5). Patients who were admitted or treated on outpatient basis from January 2009 to January 2010 have been included in this study based on inclusion and exclusion criteria. All patients were started on Intravenous Zolendronic acid after a BMD scan with T-score less than -2.5. As defined by WHO in osteoporosis, Inj. Zolendronic Acid was given once a year for 3 years.*

Results: *The mean age for the study group was 67.7 years of age (range 54 to 85 yrs). 12 patients in our study had improvement in BMD (t-score), of which 10 patients were females and 2 patients were males (all below the age of 65years). Among the 12 patients who had improvement in BMD proven by DEXA Scan, the percentage of actual improvement in BMD in these patients was an average of 11.62%.*

Conclusion: *Intravenous Zolendronic acid once every year has the best benefit when administered to osteoporotic individuals < 65yrs of age to improve BMD. Due to the better compliance of IV Zolendronic Acid, once yearly dose is preferable, when compared to oral Bisphosphonates.*

Key words: *Zolindronic acid, Osteoporosis, Dexa scan, Fragility fractures.*

INTRODUCTION

Osteoporosis a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk[1]. Early diagnosis is essential in preventing prolonged morbidity and improving the quality of life of the patient. From last two decades pharmacological and non-pharmacological treatment (usually based on physical exercise) options have been largely developed to reduce the risk of fractures in osteoporotic patients[1]. Bisphosphonates are synthetic analogues of naturally occurring pyrophosphates approved for the treatment of osteoporosis. We present our study to analyze the effect of Intravenous zolendronic therapy in osteoporotic individuals using the Dual Energy X-ray Absorptiometry Scan.

MATERIALS AND METHOD

This study was conducted at the Department of Orthopedics, Devadoss Multispecialty Hospital, Madurai. Patients who were admitted or treated on outpatient basis from January 2009 to January 2010 have been included in this study based on inclusion and exclusion criteria. This is a prospective study.

All patients above 50 yrs of age with osteoporosis measured by DEXA Scan of Lumbar Spine BMD (T-score <-2.5) which was taken as the representative and with or without fragility fractures, which were operated or conservatively managed. Further DEXA Scan showing lumbar spine BMD was done every year until a total of 4 scans (0 – baseline; 1, 2, 3 – 1st, 2nd & 3rd yr of treatment). All patients were informed regularly and followed in the outpatient department of the hospital every year for maximum period of 3 years and assessed accordingly. The recruitment was done consecutively.

Patients who had secondary osteoporosis like drug induced osteoporosis, malignancy etc, Patients with renal compromise testing (Blood Urea > 45 mg %, Serum creatinine > 1.2 mg %), those with previous use of Parathyroid Hormone, anabolic steroids or growth hormone use within 6 months prior to entry into the study and oral or intravenous systemic corticosteroids within 12 months of the study, those with any previous use of Strontium and patients with any cardiac problems such as previous history of angina, irregular rhythms or heart blocks were all excluded from the study.

A total of 36 patients with osteoporosis by WHO Criteria were included in the study (Table 1). Four patients were lost to follow-up. Two patient died due to causes not related to the surgery **(**Table 2).

Table 1: WHO diagnostic categories for BMD

Diagnostic category	Description	T score
Normal	BMD is not more than 1 SD below young adult mean value	T ≥ - 1.0
Osteopenia	BMD is between 1 and 2.5 SD below young adult mean value	T < - 1.0 to > - 2.5
Osteoporosis	BMD is 2.5 or more SD below young adult mean value	T ≤ - 2.5
Established osteoporosis	BMD is 2.5 or more SD below young adult mean value and a prevalent fragility fracture	T ≤ - 2.5

Table 2: Recruitment and Follow up Details

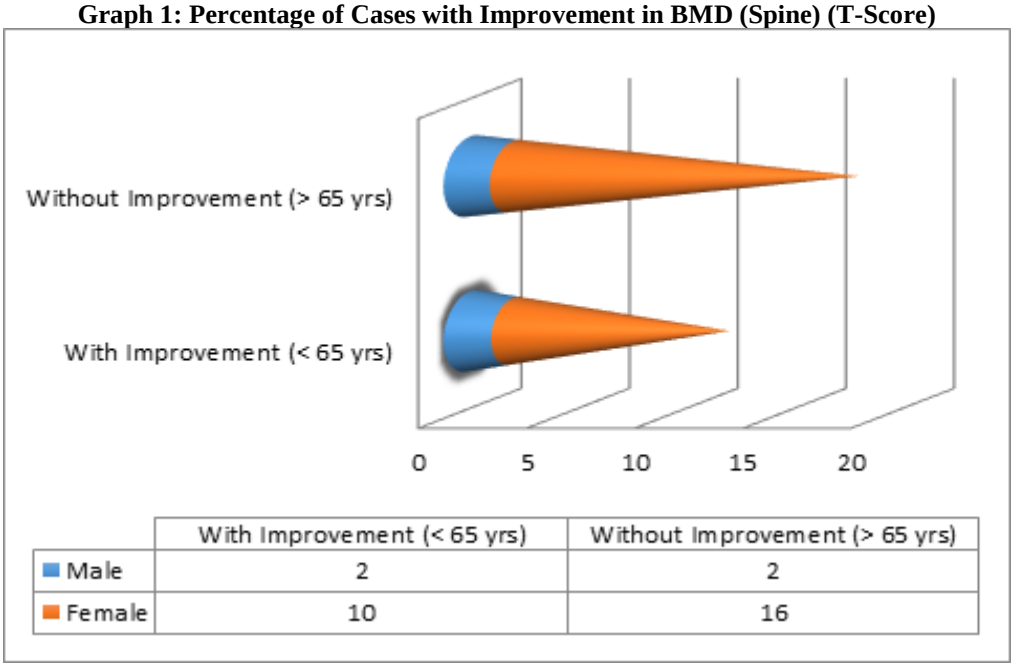
Year	Follow Up	Total Patients	Loss of Follow Up	Follow Up %
January 2009-10	Recruitment year	36	-	
Feb 2010-11	1st Year	34	2	94%
Feb 2011-12	2nd Year	33	1	92%
Feb 2012- Jan 2013	3rd Year	30	3	83%

All patients were started on Intravenous Zolendronic acid after a BMD scan with T-score less than -2.5. As defined by WHO in osteoporosis, Inj. Zolendronic Acid was given once a year for 3 years. All patients given regular calcium and weekly Inj. Vitamin D3 and advised physical exercises. Patients were yearly assessed for improvement of BMD (T-score) by using DEXA Scan and given Intravenous Zolendronic Acid and any incidence of new fractures. Based on previous studies while evaluating study results of T-score improvement <5% is considered as insignificant.

RESULTS

Of the total 36 recruited, at the time of final follow up 30 patients with completion of therapy were available for analysis. Twenty six were women and 4 were men in this study (Female: Male ratio=6.5:1). Two patients died due to various medical co – morbidities and 4 patients were lost to follow-up. The mean age for the study group was 67.7 years of age (range 54 to 85 yrs). 12 patients in our study had improvement in BMD (t-score), of which 10 patients were females and 2 patients were males (all below the age of 65years). Thus, percentage of patients with improvent in BMD (T-score) in our study was 40% of the total study group. (Graph 1)

Graph 1: Percentage of Cases with Improvement in BMD (Spine) (T-Score)



Among the 12 patients who had improvement in BMD proven by DEXA Scan, the percentage of actual improvement in BMD in these patients was an average of 11.62%. None of them sustained any further fracture during the follow up. All patients were below 65yrs of age. 5 patients had improvement no more than 5 %, 4 had no change in their BMD and 10 had worsening of BMD.

Among the 30 patients, 3 patients (10%) developed side effects like generalized body ache, fever and malaise on infusion of zolendronic acid, which subsided with conservative measures. The second dose failed to produce such symptoms in these patients. In our study 4 cases was associated with hypothyroidism of which 1 case showed improvement in BMD. 3 cases did not show any improvement or worsening of BMD. In the study group 2 patients sustained another fracture during the course of treatment. These patients were above 70 yrs of age, female sex, associated with hypothyroidism and worsened BMD.

DISCUSSION

Osteoporosis is a state of physiological decrease in bone mass that every individual passes through and they are more prone for fragility fractures at weakest portions like distal radius, fracture neck of femur, inter-trochanteric fracture, vertebral fracture to name few. Osteoporosis is called a "silent disease" because it progresses without symptoms until a fracture occurs. Because of involvement of larger skeletons and no period of rapid hormonal change, osteoporosis progresses more slowly in men than in women[2]. The fractures caused by osteoporosis have a great impact on public health, as they are often associated with increased morbidity, mortality and high economic cost. Thus, in the last two decades pharmacological and non-pharmacological treatment (usually based on physical exercise) options have been largely developed to reduce the risk of fractures in osteoporotic patients[3]. World Health Organisation (WHO) has proposed a BMD of 2.5 Standard Deviation (SD) below the average peak adult

BMD as a means of defining osteoporosis[4]. This lead to the development of the "T score" which expresses a patient's BMD in terms of the number of Standard Deviations above or below the average peak adult BMD.

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to increased bone fragility, thus increasing the susceptibility to fracture. It is an important public health problem leading to an increased risk of developing spontaneous and traumatic fractures. In India, osteoporotic fractures occur more commonly in females and occur at a younger age than in the western countries. Loss of independence is a major fear of the elderly, with 80% of women above the age of 75 preferring death to being housed at a health care facility as a result of a hip fracture[5]. Fractures of the hip, spine or wrist have been found to affect quality of life to a degree that is similar to that seen in other serious chronic diseases such as asthma, chronic obstructive pulmonary disease and osteoarthritis[6]. So prevention and treatment of osteoporosis has become important in orthopaedic practice. Besides nutritional supplements like Calcium and Vitamin D, the most commonly prescribed drugs are Bisphosphonates which are used to treat osteoporosis in many other countries including India.

Alendronate, a once daily oral medication, was the first Bisphosphonate to be approved for treatment of osteoporosis in the US in 1995. Risedronate is an oral medication that can be administered daily, weekly or monthly at varying doses. Zolendronic Acid is the newer medication which is administered once yearly by Intravenous transfusion[6]. Zolendronic Acid, a Third generation bisphosphonates with 100% Bioavailability, imidazole side chain. This confers potency two or three orders of magnitude greater than Non nitrogenous Bisphosphonates. The relatively long duration of action of zolendronic acid is attributable to its high binding affinity for bone mineral. Reduces risk of Vertebral fracture by 70 %; hip fracture by 40%. Out of all Bisphosphonates, Zolendronic acid has the highest affinity for binding to the bone mineral matrix followed by pamidronate[7]. Bisphosphonates with higher affinity like zolendronic acid bind avidly to the bone surface but, spread through bone slowly whereas lower affinity agents like clodronate distribute more widely through the bone, but they have shorter time of residence when the treatment is stopped. Suppression of bone resorption occurs within approximately three months of initiation of oral Bisphosphonate therapy regardless of dosing frequency; however it is more rapid after intravenous administration[7]. Many patients who receive prescriptions for oral Bisphosphonates stop treatment and most appear to be taking less than 80% of their prescribed pills at 12 months[8]. Adherence to a regimen of oral Bisphosphonates is challenging because the drug must be taken with a full glass of water when the patient is fasting and the patient must remain upright for at least 30 minutes after taking the medication. Since poor adherence reduces the antifracture efficacy[8]. A single annual infusion of zolendronic acid improve such efficacy in clinical practice. After three years of treatment, Bisphosphonates have shown to increase BMD of the hip by 3 - 6% and at the spine by 5 - 8%. Bisphosphonates reduce the risk of vertebral and hip fractures by up to 60%, depending on the specific Bisphosphonate and regimen[9]. The most dramatic effect is the reduction in the risk of sustaining multiple spine fractures, which has been decreased by 84% in alendronate studies[10]. This shows that treatment can dramatically reduce the progression of fractures in patients at increased risk as a result of prior fractures. Bisphosphonates were shown to reverse bone loss, with alendronate increasing bone mineral density in the spine by an average of 11% and 14% by seven and ten years respectively[11,12].

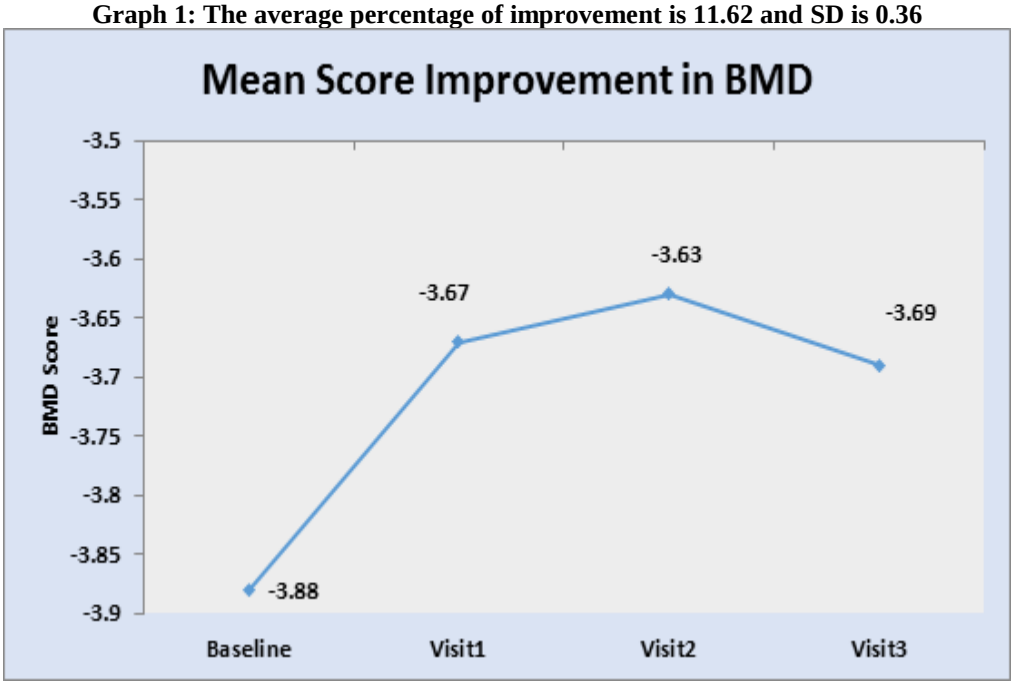
Increased bone mineral density and reduced bone turnover from Bisphosphonate treatment have been extensively documented. Bone mineral density, as estimated with DEXA, was shown to increase most in the spine (Up to 5% in the first year), which contains a relatively large component of cancellous bone, with a similar increase in the trochanter and a somewhat lower increase in the femoral neck, which has a higher content of cortical bone[9]. In women with osteoporosis zolendronic acid, alendronate and risedronate also reduced non-vertebral fractures by 25 - 40%, including hip fractures by 40 - 60%[13]. By taking consideration of all advantages and efficacy of IV Bisphosphonates, in our study we prescribed IV Zolendronic Acid infusion. This was mainly because of poor compliance of patients to oral Bisphosphonates due to irregular dosing, missing regular intake of the drug, too frequent dosing, irregular follow up, gastro esophageal complications and cost of the drugs. They were evaluated by DEXA Scan yearly for 3 yrs. According to Black et al once a year Zolendronic Acid for treatment of postmenopausal osteoporosis showed improvement of 6.71% BMD in spine (DEXA evaluation)[14]. Watts Et al found, long-term use of bisphosphonates in osteoporosis to impove 5 – 8% in spine BMD per year[13]. In our study, 40% of the study population showed significant improvent in BMD (t - score) of about 11.62% (DEXA evaluation) (P= 0.043, <0.05) (Table3) (Graph1). Rest of 60% did not show significant Improvement (> 5% increase in BMD) or showed actual worsening in spine BMD. In all patients above the age of 65yrs no improvement was noted, which was due to various factors, adequate exposure to sunlight. As per our study it was found that, Percentage improvement in females - 38.5 % compared to males who had 50% improvement($p>0.05$). In our study, 87% population already sustained fractures included in study population. 8% sustained second fracture during our study. Rest 13% cases did not sustain a fracture during the study period. Our findings are comparable to Black et al study in which yearly zolendronic acid for treatment of postmenopausal osteoporosis showed 8% clinical fractures[14].

Table 3

BMD	Mean	SD	P-Value
Baseline	-3.88	0.13	
Visit1	-3.67	0.13	<0.001
Visit2	-3.63	0.74	<0.001
Visit3	-3.69	0.88	0.043

Paired t - test was used to find the significance difference the baseline and each follow up is showing statistically significant.

Graph 1: The average percentage of improvement is 11.62 and SD is 0.36



Adverse effects /complications include renal, esophageal, and Acute Phase Reactions. Approximately 18% of patients receiving first doses of IV Bisphosphonate experience an acute phase reaction (fever, headache, myalgia, arthralgia, malaise) occurring within 24 – 36 hrs and lasting up to 3 days. The incidence is reduced approximately 50% by Acetaminophen (500 – 1000 mg before and for 24–48 h after infusion) and decreases with subsequent infusions. Atrial fibrillation, Osteonecrosis of the jaw, Atypical Subtrochanteric fractures are the other rare and serious complications. In our study 10% cases showed adverse effects like generalized body aches and fever. 10% cases showed adverse effects after 1st infusion and 6.6% in 2nd infusion. No effects were seen after the 3rd infusion. According Black et al. Study once-yearly zolendronic acid for treatment of postmenopausal osteoporosis showed 31.6%, 6.6%, 2.8% after 1st, 2nd, 3rd infusions of zolendronic acid respectively[14]. There was a 3.7% incidence of cardiac events and 2.8% incidence of stroke in the above mentioned study but there were no serious complications in our study. Our results were similar to Black et al. Study in which 16.1% cases had fever and 9.5% cases of myalgia during the first infusion[14]. Bisphosphonate - induced reduction of bone turnover is associated with increased BMD, shown to be due in part to improved mineralization and crystal formation[15]. Which is believed to contribute to the increase in bone strength. Increased bone strength following treatment has been documented in experimental animals by ex vivo biomechanical testing[16]. Bone resorption inhibitors such as Bisphosphonates are thought to increase bone mass by filling in the 'remodelling' space. Osteoclastic resorption lasts about three weeks and is followed by Osteoblastic bone formation which lasts three to four months. This time difference predicts that if resorption is stopped or slowed, bone mass will increase for several months while the resorbed space fills in and the emerging resorption space is reduced. The finding that the largest increase in bone mass is produced by Bisphosphonates during the first six months of therapy and in bones with the highest rate of remodelling is consistent with this. Several hypotheses have been proposed to explain the increase in bone mass beyond the period necessary for filling of the remodelling space: Increase in parathyroid hormone levels caused by small reductions in serum calcium levels, positive bone balance produced by a longer bone formation period, higher mineral content, direct effects of resorption inhibitors on bone formation. The ability to reduce fracture frequency appears to be due to both reduction in activation frequency as well as increased bone density. And is reflected in the reduction in fracture risk observed in clinical trials, as noted above.

When compared to Black et al Study, the therapeutic validity of the improvement in BMD in our study is higher. Hence it can be inferred that bone strength increases preventing further fragility fractures[14]. Although our sample size is low it's very difficult to determine the efficacy of IV Zolendronic Acid to have a therapeutic effect on improving BMD in osteoporotic patients. It

should however be used judiciously keeping in mind of its adverse effect.

CONCLUSION

Intravenous Zolendronic acid once every year has the best benefit when administered to osteoporotic individuals < 65yrs of age to improve BMD. Due to the better compliance of IV Zolendronic Acid, once yearly dose is preferable, when compared to oral Bisphosphonates. Its higher affinity to bone also plays a part improvement of BMD. Significant improvement in BMD and reliable prevention of further fractures may be achieved with yearly doses of intravenous zolindronic acid given for three consecutive years. In addition to DEXA, other investigation like bio-chemical markers of bone turnover and bone biopsy can be used for accurate diagnosis. However, due to its escalated costs (markers) and non-compliance due to post-surgical pain (bone biopsy), these procedures are not popular, even though they may be more helpful.

REFERENCES

1. Anon. Consensus Development Conference on Osteoporosis. Am J Med. 1993 Jun;94(6):646-50.
2. Osteoporosis in Men, http://www.niams.nih.gov/health_info/bone/osteoporosis/men.pdf,2010.
3. Lirani-Galvão AP, Lazaretti-Castro M. Physical approach for prevention and treatment of osteoporosis. Arq Bras Endocrinol Metabol 2010;54(2):171-8.
4. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ et al. for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729-38.
5. Klibanski A, Adams-Campbell L, Bassford T, et al. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285:785–795.
6. Waalen J. Current and emerging therapies for the treatment of osteoporosis. J Exp Pharmacol 2010;2:121-34.
7. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-45.
8. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22.
9. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333-40.
10. Levis S, Quandt SA, Thompson D, Scott J, Schneider DL, Ross PD, Black D, Suryawanshi S, Hochberg M, Yates J. Alendronate reduces the risk of multiple symptomatic fractures: results from the fracture intervention trial. J Am Geriatr Soc. 2002;50:409-15.
11. Emkey R, Reid I, Mulloy A, Correa-Rotter R, Favus M, Bone H, Gupta J, LaMotta A, Santora A. Ten-year efficacy and safety of alendronate in the treatment of osteoporosis in postmenopausal women. J Bone Miner Res. 2002;17 Suppl 1:S139.
12. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, Bone HG, Santora AC, Wu M, Desai R, Ross PD. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. J Clin Endocrinol Metab. 2000;85:3109-15.
13. Watts N.B, Diab D.L. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010; 95:1555-65.
14. Black DM, Delmas PD, Eastell R, et al. Once-yearly zolendronic acid for treatment of postmenopausal osteoporosis. N Engl J Med.2007;356:1809–1822.
15. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, Bone HG, Santora AC, Wu M, Desai R, Ross PD. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. J Clin Endocrinol Metab. 2000;85:3109-15.
16. Toolan BC, Shea M, Myers ER, Borchers RE, Seedor JG, Quartuccio H, Rodan G, Hayes WC. Effects of 4-amino-1-hydroxybutylidene Bisphosphonate on bone biomechanics in rats. J Bone Miner Res. 1992;7:1399-406.