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Original Research Article

A prospective, randomized and double blind once-monthly oral Ibandronate and Risedronate in post-menopausal osteoporosis leprosy patientsShailesh Nagpure^{*1}, Ranjana Kale², Swanand Pathak¹ and Satyavan Patel¹¹Department of Pharmacology, Jawaharlal Nehru Medical College, Sawangi, Wardha, India²Department of Pharmacology, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, India

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***Correspondence Info:**Dr. Shailesh Nagpure
Department of Pharmacology,
Jawaharlal Nehru Medical College,
Sawangi, Wardha, India***Article History:****Received:** 17/11/2017**Revised:** 24/11/2017**Accepted:** 24/11/2017**DOI:** <https://doi.org/10.7439/ijbar.v8i11.4474>**Abstract****Objectives:** The aim of the current investigation was to compare relative efficacy, tolerability and adherence of once monthly regimen of oral Ibandronate and Risedronate in postmenopausal osteoporotic leprosy patients with its impact on severity of the disease and quality of life.**Method:** This double blind, comparative study was conducted among 200 postmenopausal osteoporotic leprosy patients. The enrolled participants were screened for various diagnostic parameters. The participants were randomized in a 1:1 ratio to receive either oral Ibandronate (150 mg single tablet- once monthly) or oral Risedronate (150 mg single tablet- once monthly) for a period of one year.**Results:** Present study showed that treatment with both Ibandronate and Risedronate increased hip BMD, and Z-test with repeated measurements was used to examine the significance of the longitudinal changes in the BMD. The difference in the efficacy of the two drugs in increasing hip BMD might be attributed to the greater efficacy of Ibandronate in reducing bone turnover than that of Risedronate.**Conclusion:** Once monthly Ibandronate has a potential to decrease the severity of osteoporosis as compared to once monthly Risedronate. Also, the quality of life in terms of general health status, physical activity and pain, limitation in daily activity and the emotional status in postmenopausal osteoporotic leprosy patients is better with Ibandronate than that of Risedronate.**Keywords:** Post-menopausal, osteoporosis, leprosy, Ibandronate Risedronate.**1. Introduction**

As per NIH, Osteoporosis, an established and well-defined disease, affects more than 75 million people in the United States, Europe and Japan. Osteoporosis causes more than 8.9 million fractures annually. In India the number of osteoporosis patients were approximately 26 million (2003 figures) with the numbers projected to increase to 36 million by 2013 [1].

Osteoporosis renders spongy bones, and results into more frequent fractures, not always confines to, but usually in bones of spine, wrists and hips [2].

Bone density in an individual is maximum at 25 years, and is known to decline after 35 years at a rate of 0.3-0.5% per year. Estrogen is an important hormone in maintaining bone density in women when drops after menopause there is loss of bone density accelerates. During the first 5 to 10 years after menopause, women can suffer up to 2%-4% loss of bone density per year. The accelerated bone loss after menopause is a major cause of osteoporosis in women, referred to as "Postmenopausal osteoporosis". Prominent risk factors include genetics, lack

of exercise and calcium and vitamin D, previous history of fracture, cigarette smoking, excessive alcohol consumption, history of rheumatoid arthritis, low body weight, and family history of osteoporosis.

Leprosy includes long-term altered bony architecture, as a marked orthopedic complication, characterized by loss of bone mass. Its etiopathogenesis is multi-factorial, and further studies are needed to determine the most efficient way to prevent fractures in this condition [3]. No studies describing the relationship between bone mass and level of bone mineral density, its effective treatment, adherence to treatment and desired changes in quality of life have been reported in postmenopausal osteoporotic Leprosy patients.

Bisphosphonates are considered the first line therapy for postmenopausal osteoporosis and have proven clinical benefits, including a significantly reduced risk of vertebral and non-vertebral fractures in many clinical trials [4-8].

Ibandronate is a potent, new aminobisphosphonate, effective and well tolerated currently approved daily regimen in postmenopausal osteoporosis [8]. Numerous studies have proven that weekly dosing improves therapeutic adherence, though it remains suboptimal [9-11]. A comparative study proved monthly oral Ibandronate was as effective and well tolerated as that of daily currently approved regimen [8].

Risedronate is also widely prescribed once weekly regimen for treatment of postmenopausal osteoporosis. Comparative study between once monthly Ibandronate and once weekly Risedronate showed reduction of bone turnover marker and fewer upper GI adverse events in Ibandronate group [12]. Considering all these factors this study has been planned to compare the efficacy of available antiresorptive agents (Ibandronate and Risedronate) which are approved for once monthly dosing regimen so as to improve the adherence, in postmenopausal leprosy patients who are highly prone for repeated trauma and fragility fractures due to osteoporosis and to assess the Quality of Life of patients who are deprived of needed essential care.

The aim of the current investigation was to compare relative efficacy, tolerability and adherence of once monthly regimen of oral Ibandronate and Risedronate in postmenopausal osteoporotic leprosy patients with its impact on severity of the disease and quality of life and to assess the treatment adherence of Ibandronate and Risedronate with once a monthly regimen, and quality of life of the osteoporotic postmenopausal leprosy patient after the treatment regimen.

2. Materials and Methods

2.1 Patients

The study was conducted at one of the Rural Rehabilitation Centre for Leprosy patients in central India, where the patients of Leprosy are relocated from various states of India and in the Department of Pharmacology of tertiary care teaching hospital in central India. At this rehabilitation center, approximately 5000 Leprosy patients were rehabilitated and among them, all patients who belong to geriatric age group as well as postmenopausal women are routinely screened for various non-communicable diseases like hypertension, diabetes mellitus, cancer, osteoporosis etc.

In this study, postmenopausal women eligible for inclusion and diagnosed as osteoporosis with the help of Bone Mineral Densitometry were enrolled as a study participant after obtaining informed written consent.

The study protocol and written information to be provided to the patients were submitted to the local Regulatory Authority of Rehabilitation Center. Study protocol was approved by the Institutional Ethical Committee. The study was conducted in accordance with Good Clinical Practice Guidelines of the International Conference on Harmonization (ICH) and the principles of the Declaration of Helsinki.

The present investigation involves prospective, randomized, double blind, comparative study to investigate efficacy, tolerability and adherence between once monthly oral regimen of Ibandronate and Risedronate in postmenopausal osteoporotic leprosy patients.

2.2 Inclusion criteria

Diagnosed postmenopausal patients of osteoporosis, Patients with diagnosis component of new/old-leprosy, Patients willing to give informed written consent for participation in study, Patients with normal renal function.

2.3 Exclusion criteria

Active infection of feet, Smokers, Patients already under treatment of osteoporosis, Prior use of oestrogen replacement therapy and glucocorticoids, Gastroesophageal reflux disease, Severe anaemia, any abnormalities in laboratory parameters such as Sr. Calcium or Kidney function test, Renal disease that might affect bone and calcium metabolism, Amputated lower limbs, Bedridden Patients, Lack of consent for participation in study

2.4 Study design

This double blind, comparative study was conducted among Two Hundred (200) Postmenopausal osteoporotic leprosy patients from October 2010 to October 2011.

All Postmenopausal women of Leprosy Rehabilitation Centre were screened for osteoporosis with the help of Bone Mineral Densitometry. After screening, 246 patients were diagnosed as osteoporosis. After applying inclusion and exclusion criteria, only 204 patients were eligible as participants in this study.

All the eligible participants were informed regarding the study protocol, the disease osteoporosis, follow up screening and study drugs with all the prescribing instructions.

Out of 204 eligible participants, written consent was given by 200 participants who were hence enrolled in the study.

By using standard laboratory techniques, the enrolled participants were screened for complete blood count, serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine and lipid profile as a baseline screening by withdrawing blood from median cubital vein under all aseptic precautions. Also, all the patients were interviewed for the baseline assessment in terms of medical history and physical examination [12]. Radiograph of left hip joint was done for the assessment of severity of osteoporosis with the help of Singh's index [13]. All these tests were repeated at every follow up visit. Follow up screening were done after six months and one year of baseline study.

After enrolment and baseline screening the participants were randomized in a 1:1 ratio to receive either oral Ibandronate (150 mg single tablet- once monthly) or oral Risedronate (150 mg single tablet- once monthly) for a period of one year.

Randomization was done using block randomization technique and the patients were divided into two groups i.e. Group A (received Ibandronate once a monthly regimen for one year) and Group B (received Risedronate once a monthly regimen for one year).

2.5 Measurement of Bone Mineral Density (BMD):

BMD was measured by using DXA (Dual energy X-ray absorptiometry) for diagnosis of osteoporosis [14]. The outcome was measured by T-score which was mentioned in the form of Standard Deviation (SD) from the expected BMD of young adult of the same sex.

For interpretation of BMD results, widely used WHO study group's definitions, which are based on a comparison of a patient's BMD with the mean for a normal young adult population of the same sex and age are adapted [15,16]. The patient is assigned a "T-score," which is the number of standard deviations above or below the mean BMD for normal young adults as follows:

1) Normal BMD is defined as a T-score between +2.5 and -1.0

2) Osteopenia (low BMD) is associated with a T-score between -1.0 and -2.5 inclusive.

3) Osteoporosis is defined as a T-score lower than -2.5.

4) 4th category "severe osteoporosis" to describe patients whose T-score is below -2.5 and who also have suffered a fragility fracture.

2.6 Assessment of severity of osteoporosis:

For severity assessment, Singh's Index of radiograph (X-ray) of hip joint was considered as acriterion. The radiographs were confined to left hip joint with neutral flexion, abduction and 15° internal rotation in anteroposterior view.

The grades (between VI to I) were ascertained with the help of two orthopedicians separately, using reference radiographic charts of Singh's Index method.

Grade VI: All the normal trabecular groups are visible and the upper end of the femur seems completely occupied with cancellous bone.

Grade V: The structure of principal tensile and principal compressive trabeculae is accentuated. Ward's triangle appears prominent.

Grade IV: Principal tensile trabeculae are markedly reduced in numbers but can still be traced from lateral cortex to upper part of femoral neck.

Grade III: There is a break in continuity of the principal tensile trabeculae.

Grade II: Only the principal compressive trabeculae stand out prominently, the others have been more or less completely resorbed.

Grade I: Even the principal compressive trabeculae are markedly reduced in number and no longer prominent. On the basis of Singh's Index grading system, severity of the disease was assessed.

2.7 Blinding of drugs and assessment

The study drugs were procured from different pharmaceutical companies in the form of tablets. Tablet Ibandronate 150 mg was procured from Dr. Reddy's Lab., and Tablet Risedronate 150 mg was procured from Cipla Pharmaceutical Ltd.

Drugs were distributed by the Nursing staff to the study subjects. Records were maintained by Nursing staff regarding dosing schedule, dose received by the study participants and adverse events in view of evaluation of the treatment adherence and tolerability.

Quality of Life of postmenopausal osteoporotic leprosy patients was assessed with the help of Semi-structured, Pre-Designed, Pretested Questionnaire based on the ECOS-16 questionnaire in both the study groups at the end of one year of treatment [15].

Quality of life was assessed under four heads which are as follows:

- 1) Patients general health status
- 2) Physical activity and pain
- 3) Limitation in daily activity
- 4) Change in emotional status.

Out of the total 18 questions, first two were asked to assess general health status and next five were intended to assess the physical activity and pain. Limitation in daily activity was assessed by the responses to question no. 8 to 13 while responses to question no. 14 to 18 reveal us the changes in emotional status of the patients. The mean score of the responses to the questions in each domain was calculated for every patient, and the mean of these individual scores was then determined for respective heads to compare the quality of life in group A and group B.

Questionnaire had a single scoring design for all of the items. All items had five possible response options. The score of each item ranged from 1 to 5, indicating quality of life from “Much better” to “Much worse” (1= Much better, 2= Better, 3= More or less the same, 4= Worse and, 5= Much worse). So, lower the score in each dimension, the better is the quality of life [16].

2.8 Analysis

Data were collected by mean of Case Record Form (Annexure III) and Statistical Analysis was done by using descriptive statistics and inferential statistics using student paired t-test, Chi-square test and Z-test. The software used in the analysis was SPSS 17.0 and Graphpad prism 5.0. All the results were tested at 5% level of significance.

3. Results

The study was conducted at the Rural Rehabilitation Centre for Leprosy patients in central India, and in the Department of Pharmacology of tertiary care teaching hospital in central India to compare the efficacy, tolerability and adherence between once monthly oral regimen of Ibandronate and Risedronate.

After screening, 200 postmenopausal osteoporotic leprosy patients were enrolled in this study who were randomized to Group A and Group B. Participants in Group A, i.e. Ibandronate group and Group B, i.e. Risedronate group were matched for characteristics like age, weight, height, body mass index, duration of menopause and disease duration of leprosy. No significant difference observed between Group A and Group B ($p > 0.05$) and hence was comparable to avoid the bias in study as shown in Figure 1.

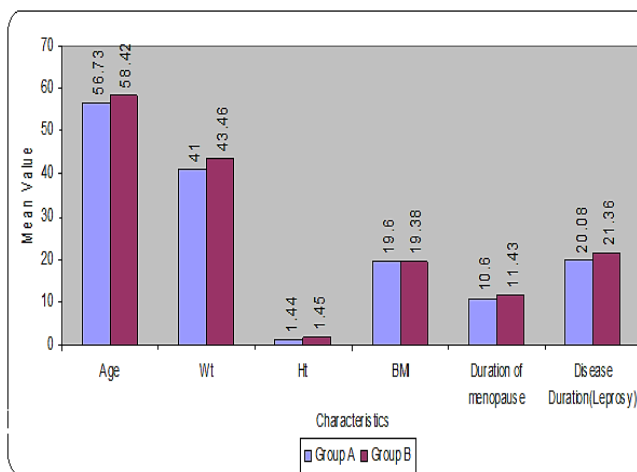


Figure 1: Characteristics of study subjects

Figure 2 shows that mean T-score of BMD in Group A at baseline was -3.17, at 6 months -2.89 and at 12 months -2.71 showing increase in BMD compared to baseline whereas mean T-score of BMD in Group B at baseline was -2.82, at 6 months -2.66 and at 12 months -2.51 also shows increase in BMD compared to baseline at both follow up visits.

The percent change in the hip BMD at first follow up visit between Group A and Group B was statistically significant (8.83% increase in BMD in Ibandronate group and 5.67% increase in BMD in Risedronate group ($p < 0.05$)). Also, there was significant difference in the % change in the hip BMD at second follow up visit, between Group A and Group B (14.51% increase in BMD in Ibandronate group and 10.99% increase in BMD in Risedronate group ($p < 0.05$)).

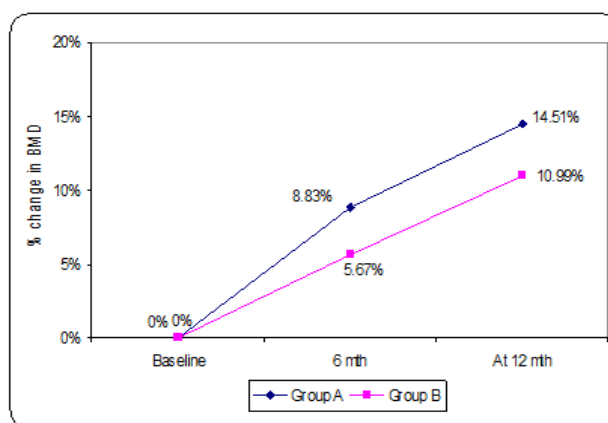


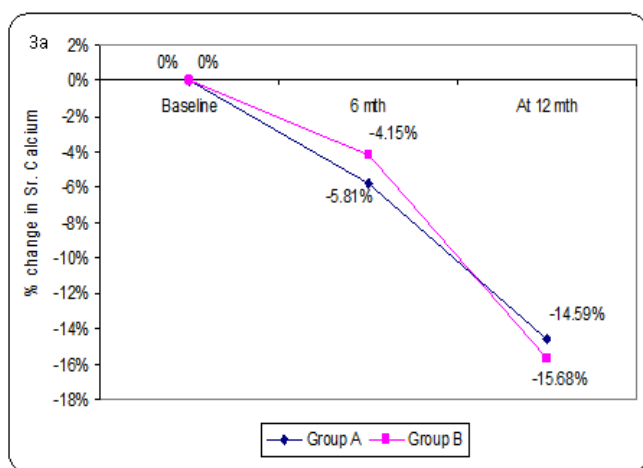
Figure 2: Comparison of BMD (T-Score) at baseline, at 6 months and at 12 months of treatment in Group A and Group B

Figure 3a indicates mean serum calcium level in group A at baseline was 9.46 mg/dl which decreased to 8.91 mg/dl at 6 months and further it was decreased to 7.61 mg/dl at the end of one year of treatment with Ibandronate. Similarly, in group B the mean serum calcium level was 9.38 mg/dl at baseline which consistently decreased to 8.99 mg/dl and 7.58 mg/dl at 6 months and one year respectively on treatment with Risedronate.

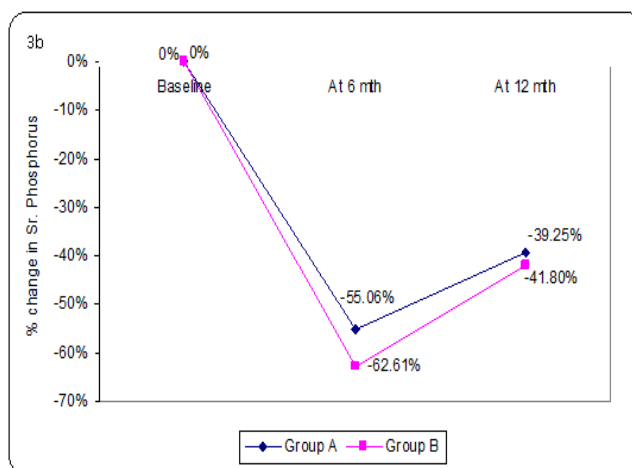
Figure 3b indicates mean serum phosphorus level in group A at baseline was 5.63 mg/dl which increased to 8.73 mg/dl at 6 months but at the end of one year of treatment with Ibandronate the mean serum phosphorus level was greater than that of baseline and less than that of 6

months i.e. 7.84 mg/dl. Similarly, in group B the mean serum phosphorus level was 5.43 mg/dl at baseline which increased to 8.83 mg/dl at 6 months and further it was decreased to 7.70 mg/dl at the end of one year of treatment with Risedronate.

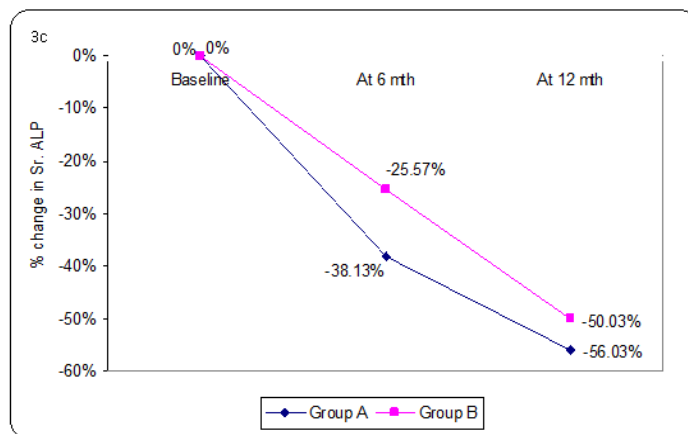
Figure 3c indicates mean serum ALP level in group A at baseline was 137.12 U/L which decreased to 84.82 U/L at 6 months and further it was decreased to 60.27 U/L at the end of one year of treatment with Ibandronate. Similarly, in group B the mean serum ALP level was 106.71 U/L at baseline which consistently decreased to 79.41 U/L and 53.31 U/L at 6 months and one year of treatment with Risedronate respectively.



a



b



c

Figure 3a: Comparison of serum Calcium at Baseline, at 6 months and at 12 months of treatment in Group A and Group B.

Figure 3b: Comparison of serum Phosphorus at baseline, at 6 months and at 12 months of treatment in Group A and Group B.

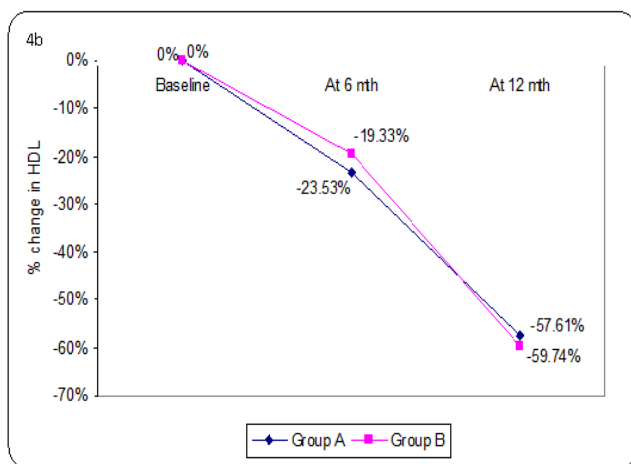
Figure 3c: Comparison of serum ALP at baseline, at 6 months and at 12 months of treatment in Group A and Group B.

Figure 4a shows that the mean total cholesterol level in group A at baseline was 219.66 mg/dl which decreased to 167.10 mg/dl at 6 months and further it was decreased to 138.71 mg/dl at the end of one year of treatment with Ibandronate. Similarly, in group B the mean total cholesterol level was 205.57 mg/dl at baseline which decreased to 162.78 mg/dl and 130.75 mg/dl at 6 months and one year of treatment with Risedronate respectively.

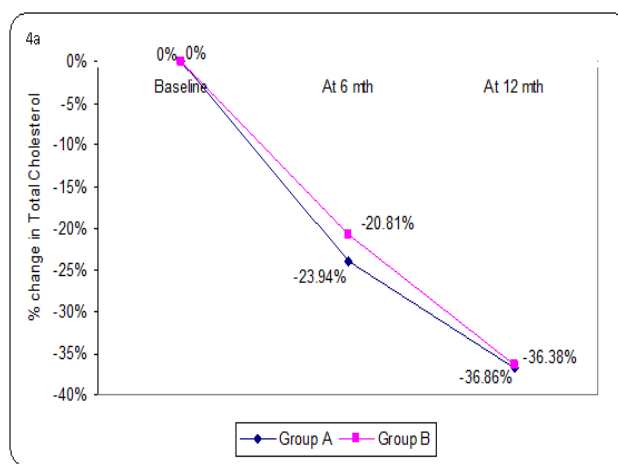
Figure 4b shows that the mean total cholesterol level in group A at baseline was 219.66 mg/dl which decreased to 167.10 mg/dl at 6 months and further it was decreased to 138.71 mg/dl at the end of one year of treatment with Ibandronate. Similarly, in group B the mean total cholesterol level was 205.57 mg/dl at baseline which decreased to 162.78 mg/dl and 130.75 mg/dl at 6 months and one year of treatment with Risedronate respectively.

Figure 4b indicates, mean HDL level in group A at baseline was 62.07 mg/dl which decreased to 47.46 mg/dl at 6 months. At the end of one year of treatment with Ibandronate the mean HDL level was less than that of normal range (40-80 mg/dl) i.e. 26.31 mg/dl. Similarly, in group B the mean HDL level was 57.81 mg/dl at baseline which decreased to 46.63 mg/dl at 6 months and further it was decreased to 23.27 mg/dl at the end of one year of treatment with Risedronate showing gradual decreased in HDL level in both the groups.

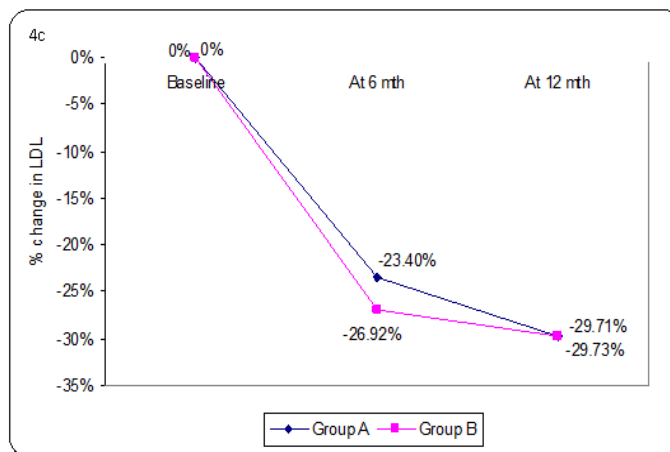
Figure 4c indicates mean LDL level in group A at baseline was 128.39 mg/dl which decreased to 98.35 mg/dl at 6 months and further it was decreased to 90.25 mg/dl at the end of one year of treatment with Ibandronate. Similarly, in group B the mean LDL level was 116.25 mg/dl at baseline which consistently decreased to 84.99 mg/dl and 82.72 mg/dl at 6 months and one year of treatment with Risedronate respectively.



a



b



c

Figure 4a: Comparison of Total Cholesterol at baseline, at 6 months and at 12 months of treatment in Group A and Group B,

Figure 4b: Comparison of HDL at baseline, at 6 months and at 12 months of treatment in Group A and Group B,

Figure 4c: Comparison of LDL at baseline, at 6 months and at 12 months of treatment in Group A and Group B

3.1 Severity assessment (Singh’s Index)

In Group A, a total of 4 patients were in Grade I and at first follow up visit, the improvement in severity grading (from Grade I to II) was observed in one patient. A total of 49 patients were in grade II severity at the baseline screening and at first visit the improvement in severity grading (from Grade II to III) was observed in one patient.

Grade III severity was observed in total of 39 patients at baseline screening. At the baseline screening a total of 8 patients were in grade IV severity. After the completion of the study, all the 8 participants showed same severity grading as baseline screening. Whereas 2 more patients showed Grade IV severity at first and second follow up visits. No patients were observed in Grade V and Grade VI

severity at baseline screening as well as in subsequent follow up visits.

In Group B, No Grade I, IV, V and VI severity was observed in any of the patient at baseline screening as well as in subsequent follow up visits. At the baseline screening, a total of 79 patients were in Grade II severity. At first follow up visit, 79 patients showed same severity grading as that of baseline screening. Whereas additional 8 patients showed Grade II severity at first follow up visit. At completion of the study there were total of 88 patients in Grade II severity. At the baseline screening a total of 21 patients were in Grade III severity. At first follow up visit only 13 patients showed same severity grading as that of baseline. Whereas 8 patients were deteriorated to Grade II from Grade III severity at first follow up visit. At the second follow up visit, only 12 patients showed Grade III severity whereas one patient was deteriorated from Grade III to Grade II severity at the end of the study.

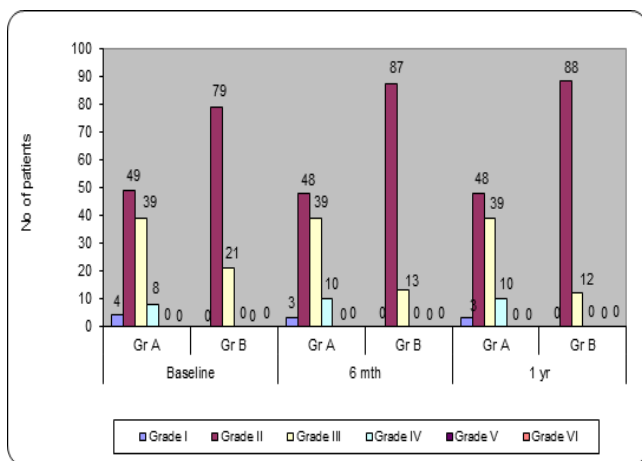


Figure 5: Comparison of X-Ray Hip (severity grading) at baseline, at 6 months and at 12 months of treatment in Group A & Group B

3.2 Quality of life

In Group B postmenopausal females described significant changes in their physical activity and back pain (3.94 ± 0.85) more worse than Group A (3.42 ± 0.81) as mentioned above. Also change in emotional status was worse in Group B postmenopausal female (3.14 ± 0.86) than Group A postmenopausal female (2.69 ± 0.81). The difference was statistically significant ($p < 0.05$).

Limitation in daily activities was also worse in Group B (3.87 ± 0.89) than Group A postmenopausal females (3.43 ± 0.76) and the difference is statistically significant ($p < 0.05$).

Figure shows that all osteoporotic postmenopausal leprosy patients in both the groups have worse Quality of Life (Total mean score= 3.45 ± 0.74) but more pronounced in Group B.

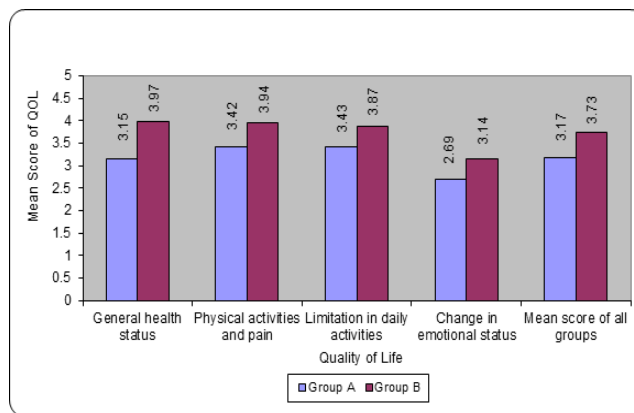


Figure 6: Mean score of Quality of Life in postmenopausal osteoporotic leprosy patients

4. Discussion

In this study, the participants of both the groups treated with Ibandronate and Risedronate once monthly regimen for 1 year were comparable in terms of age, weight, height, BMI, duration of menopause and disease duration of leprosy.

In Ibandronate treated group there was significant increase in BMD after 6 months and 12 months, and in the same way Risedronate treated group showed significant increase in BMD after 6 months and 12 months. This confirmed that these drugs are highly effective in increasing BMD after one year of treatment.

Present study showed that treatment with both Ibandronate and Risedronate increased hip BMD (14.51% and 10.99% at 12 months, respectively), Z-test with repeated measurements was used to examine the significance of the longitudinal changes in the BMD. The effects of Ibandronate were more pronounced than those of Risedronate, showing the greater efficacy of Ibandronate in increasing hip BMD through its effect to reduce the bone turnover more markedly than by Risedronate.

The difference in the efficacy of the two drugs in increasing hip BMD might be attributed to the greater efficacy of Ibandronate in reducing bone turnover than that of Risedronate. Greater the suppression of bone turnover, greater will be the increase in BMD [17-20]. Bisphosphonates inhibit osteoclast mediated bone resorption, and loss of osteoclast function and apoptosis is the consequence of loss of function of one or more important signaling proteins. In particular, nitrogen-containing bisphosphonates like Ibandronate and Risedronate are not metabolized, but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds, which are essential for post-translational modification of small GTPases [21].

Biochemical tests were performed for the assessment of efficacy of bisphosphonates. Results of this

study reveal that serum calcium level was consistently decreased from baseline to one year of treatment in both the groups but the levels were within the normal range. Serum phosphorus levels at baseline was more than that of normal limit and consistently remained higher throughout the treatment for one year in both the groups. Percent change of total cholesterol, HDL and LDL in Ibandronate group was not significant when compared with Risedronate group. In both the studies, the main effect was reduction in LDL and total cholesterol.

Present comparative evidence of, the Ibandronate group showed more pronounced reductions in severity of osteoporosis in terms of Singh's index than Risedronate group, which suggests that, there is improvement in quality of bone architecture in Ibandronate group whereas no improvement in quality of bone architecture in Risedronate group.

The present study was grounded on the assumption that osteoporotic postmenopausal leprosy patients often experience low levels of quality of life. This was substantiated by our results, where majority of females in both groups showed impairment in their QOL. Group B postmenopausal females described significant changes in their physical activity and back pain more worse than Group A. Also change in emotional status and limitation in daily activities were worse in Group B.

Osteoporosis manifests itself in different ways, including skeletal fractures, kyphosis and pain [22]. Back pain and discomfort usually presented and can influence sleep and rest pattern of the postmenopausal women [23]. This is also in agreement with Taft *et al* who reported that old elders had generally underscored physical function and severe limitations in performing daily activities [24]. This may be attributed to estrogen cessation over years and change in their lifestyle, such as reduced physical activities, mobility and exercises.

5. Conclusion

The study clearly shows that the efficacy of once monthly oral Ibandronate (150 mg) is more than that of once monthly oral Risedronate (150 mg) as there is significant increase in BMD in Ibandronate group as compared to Risedronate group. Tolerability to once monthly regimen of both the study drugs is similar, as there was no study dropout for entire one year of study duration. Once monthly Ibandronate has a potential to decrease the severity of osteoporosis as compared to once monthly Risedronate. Also, it has been proved that the quality of life in terms of general health status, physical activity and pain, limitation in daily activity and the emotional status in postmenopausal osteoporotic leprosy patients is better with Ibandronate than that of Risedronate.

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