

# Management of post-menopausal osteoporosis in leprosy patients using one-monthly oral Ibandronate administration

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## Abstract

**Objective:** To study the effects of once monthly regimen of Ibandronate on bone marrow density, severity of osteoporosis and quality of life in postmenopausal osteoporotic leprosy patients.

**Materials and Methods:** Out of 204 eligible participants, written consent was given by 200 participants who were hence enrolled for the study. These 200 patients with postmenopausal osteoporotic leprosy were administered with Ibandronate tablet (150mg) as once monthly from October 2010 to October 2011. Patients were analyzed for BMD, severity of osteoporosis and quality of life index.

**Results:** The percentage change in the hip BMD at first follow up was increased by 8.83% and with second follow up it was increased by 14.51%. A total of 4 patients were in Singh's Index Grade I, 128 patients in Grade II and 60 patients in Grade III severity at the baseline screening. No study dropouts were found for entire 1 year of treatment duration, that is 100% adherence were observed in subjects undergoing treatment.

**Conclusion:** Monthly regimen of Ibandronate confirmed having better tolerability and adherence in postmenopausal osteoporotic leprosy patients. 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 the findings, where majority of females in showed improvement in their QOL, with reference to physical activity and pain, limitations to daily activities, change in emotional status and general health status.

**Keywords:** post-menopausal, leprosy, osteoporosis, Ibandronate.

## 1. Introduction

Osteoporosis leads to unusually spongy bone that is easily compressible, lowering its functional and structural utility. This ailment of the skeleton deteriorates the bone and resulting into recurrent breakages owing to moderate injuries, not limited to bones of spine, hips and wrists [1]; Although osteoporosis-related fractures can occur in almost any skeletal bone.

Under normal growth of the body since childhood, the bones density gains optimization till the age of 25 and is upheld for further 10 years. In either sex aged beyond 35 years, the bone density declines at a rate of 0.3%-0.5% per annum, considered as a result of normal aging process.

Estrogen is an important hormone in maintaining bone density in women. When estrogen levels drop after menopause, loss of bone density accelerates. During the first 5 to 10 years after menopause, women may suffer up to 2%-4% loss of bone density per year. This can result in the loss of up to 25%-30% of their bone density during that time period. The accelerated bone loss after menopause is a major cause of osteoporosis in women, referred to as "Postmenopausal osteoporosis".

Other risk factors for development of osteoporosis include genetics, lack of exercise, lack of 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.

Postmenopausal osteoporosis may be identified during routine medical care, or in the wake of a fracture which does not heal properly and its complications, that represent a significant burden to society. Osteoporotic fractures can have a detrimental impact on an individual's level of independence, quality of life, and potential mortality. Hip and vertebral fractures lead to a greater risk of functional impairment and institutionalization [2].

Orthopedic complications in leprosy include altered bony architecture and stress leading to repeated local trauma. Leprosy is still known to cause considerable long-term orthopedic morbidity. Bone mass loss is an event in leprosy patients which occur very frequently. Its etiopathogenesis is multi-factorial, and further studies are needed to determine the most efficient way to prevent fractures in this condition [3].

Ishikawa et al studied osteoporosis in male and female Leprosy patients [4]. However, 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.

Also, Osteoporosis is a common, chronic but frequently asymptomatic disease of the skeleton associated with low rates of treatment adherence and persistence [5,6]. Although no treatment completely reverses established osteoporosis but medical intervention can halt the progression of osteoporosis.

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 [7-11].

Ibandronate is a potent, new aminobisphosphonate, effective and well tolerated currently approved daily regimen in postmenopausal osteoporosis [11]. Numerous studies have proven that weekly dosing improves therapeutic adherence, though it remains suboptimal [12-14]. A comparative study proved monthly oral Ibandronate was as effective and well tolerated as that of daily currently approved regimen [11].

The aim of the present investigation was to study the efficacy and tolerability of once monthly dosage regimen of Ibandronate, an antiresorptive agent. The objectives of the research envisaged were to study the effects of once monthly regimen of Ibandronate on bone marrow density, severity of osteoporosis and quality of life in postmenopausal osteoporotic leprosy patients.

## 2. Materials and Methods

The prospective, randomized and controlled trial for the research was carried out 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 MGIMS, Sewagram, Wardha. At this rehabilitation centre, approximately 5000 Leprosy patients were rehabilitated and among them, postmenopausal women eligible for inclusion and diagnosed as osteoporotic 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 and approved by the local Regulatory Authority of Rehabilitation Centre.

### 2.1 Study design

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 and the study was conducted among 200 Postmenopausal osteoporotic leprosy patients from October 2010 to October 2011.

### 2.2 Inclusion criteria

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

### 2.3 Exclusion criteria

- 1) Active infection of feet
- 2) Smokers
- 3) Patients already under treatment of osteoporosis
- 4) Prior use of oestrogen replacement therapy and glucocorticoids
- 5) Gastroesophageal reflux disease
- 6) Severe anaemia
- 7) Any abnormalities in laboratory parameters such as Sr. Calcium or Kidney function test.
- 8) Renal disease that might affect bone and calcium metabolism
- 9) Amputated lower limbs
- 10) Bedridden Patients
- 11) Lack of consent for participation in study

## 2.4 Methods

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 [15]. Radiograph of left hip joint was done for the assessment of severity of osteoporosis with the help of Singh's index [16]. 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 administered orally with Ibandronate (150 mg single tablet) for a period of one year, once every month on the same day at morning hours to the respective participants. The tablets were distributed by the Nursing staff to the study subjects on the first day of every month in the morning with the prior instruction to every patient and assurance of oral intake of the drug.

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.

## 2.5 Measurement of Bone Mineral Density (BMD)

BMD was measured by using DXA (Dual energy X-ray absorptiometry) for diagnosis of osteoporosis [15]. 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. 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 [17,18]:

- 1) Normal BMD is defined as a T-score between +2.5 and -1.0 (i.e. the patient's BMD is between 2.5 SDs, above the young adult mean and 1 SD below the young adult mean).
- 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) The WHO study group added a 4<sup>th</sup> 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 determination of Singh's Index, 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.

## 2.6 Assessment of quality of life

Quality of Life of postmenopausal osteoporotic leprosy patients were assessed with the help of Semi-structured, Pre-Designed, Pretested Questionnaire based on the ECOS-16 questionnaire in study groups at the end of one year of treatment [19].

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 number 8 to 13 while responses to question number 14 to 18 reveal 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 mean of these individual scores was then calculated for respective heads to compare the quality of life in group A and group B.

Questionnaire has a single scoring design for all of the items. All items have 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,  
5= Much worse

So, lower the score in each dimension, the better is the quality of life. These items were validated in previous studies.

## 2.7 Statistical Analysis

Data were collected by mean of Case Record Form 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 study the efficacy, tolerability and adherence between once monthly oral regimen of Ibandronate, and to assess the severity of disease, adverse drug events and quality of life among postmenopausal osteoporotic leprosy patients.

The data were entered into a spreadsheet (Excel, Microsoft Corp.) and treated with statistical software, SPSS 17.0 and Graphpad prism 5.0 for data analysis. Utilization of descriptive statistics and inferential statistics using student paired t-test, Chi-square test and Z-test was done. P value < 0.05 was considered statistically significant.

### 3.1 Measurement of Bone mineral density

After screening, 200 postmenopausal osteoporotic leprosy patients were enrolled in this study and were analyzed for characteristics like age, weight, height, body mass index, duration of menopause and disease duration of leprosy (Table 1).

**Table 1: Characteristics of study subjects**

| Characteristics           | Value       |
|---------------------------|-------------|
| Age (years)               | 56.73±7.54  |
| Weight (kg)               | 41±7.72     |
| Height (m)                | 1.44±0.02   |
| BMI (kg/m <sup>2</sup> )  | 19.60±3.86  |
| Duration of menopause     | 10.60±7.14  |
| Disease Duration(Leprosy) | 20.08±11.24 |

**Table 2: Descriptive statistics BMD (T-Score) at baseline (at 0 month), at 6 months and at 12 months of treatment with Ibandronate**

| Interval              | N   | Mean T- score | SD   | SEM  |
|-----------------------|-----|---------------|------|------|
| Baseline (at 0 month) | 200 | -3.17         | 0.55 | 0.05 |
| After 6 months        | 200 | -2.89         | 0.48 | 0.04 |
| After 12 months       | 200 | -2.71         | 0.54 | 0.05 |

n: number of subjects, SD: Standard Deviation, SEM: Standard error of mean

**Table 3: BMD (T-Score) at baseline (at 0 month), at 6 months and at 12 months of treatment with Ibandronate (z-value and p-value)**

| Interval              | z-value | p-value | Mean Difference | Std. Error Difference | 95% CI of the Difference |       |
|-----------------------|---------|---------|-----------------|-----------------------|--------------------------|-------|
|                       |         |         |                 |                       | Lower                    | Upper |
| Baseline (at 0 month) | 4.788   | 0.012*  | -0.34           | 0.07                  | -0.49                    | -0.20 |
| After 6 months        | 3.566   | 0.027*  | -0.22           | 0.06                  | -0.35                    | -0.10 |
| After 12 months       | 2.143   | 0.033*  | -0.19           | 0.09                  | -0.38                    | -0.01 |

CI: Confidence interval, \*p<0.05

Table 2 and Table 3, shows mean T-score of BMD at baseline was -3.17, at 6 months -2.89 and at 12 months -2.71 showing increase in BMD compared to baseline. The percentage change in the hip BMD at first follow up visit was statistically significant (8.83% increase in BMD) (p<0.05). There was significant difference in the percentage change in the hip BMD at second follow up visit (14.51% increase in BMD) (p<0.05).

### 3.2 Severity assessment by Singh's Index

A total of 4 patients were in Grade I, 128 patients in Grade II and 60 patients in Grade III severity at the

baseline screening. At the first follow up visit, the improvement in severity grading (from Grade I to II) was observed in one patient. However no further improvement in severity grading was observed at the completion of study.

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.

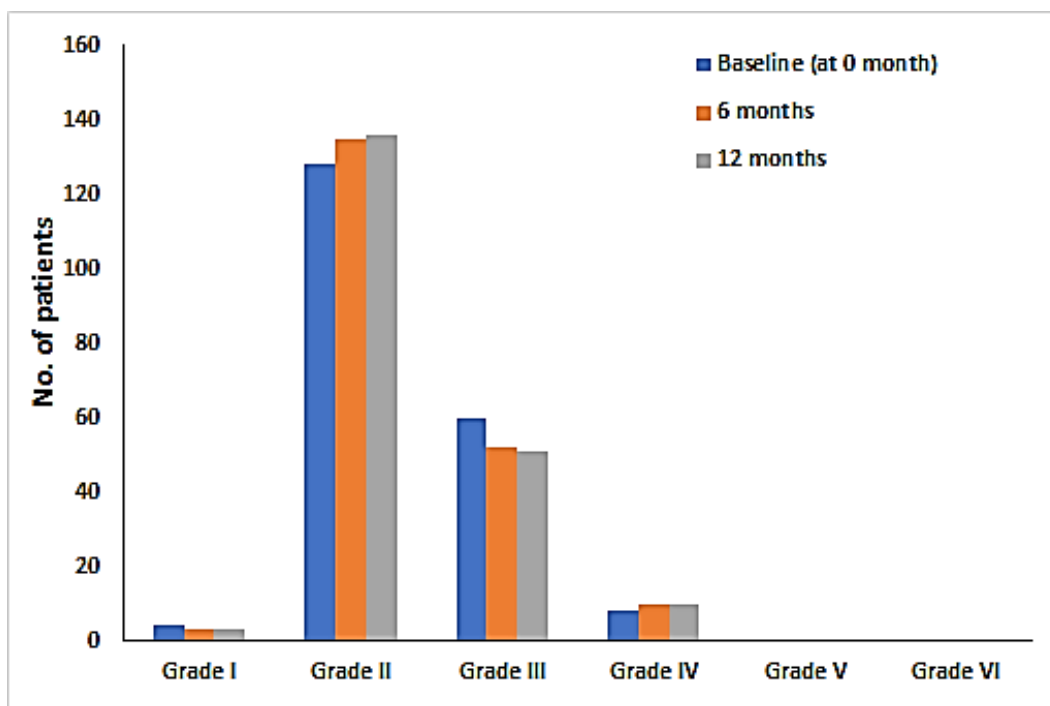


Figure 1: Severity Assessment of osteoporosis (Singh's index) comparison of X-Ray Hip (severity grading) at baseline, at 6 months and at 12 months of treatment.

### 3.3 Mean score of Quality of Life postmenopausal osteoporotic leprosy patients

A Total 42 adverse event in patients and Out of 42 adverse events, 50% were related to gastrointestinal system, 38% with musculoskeletal system and 11.9% adverse

events were related to central nervous system. In this study, no study dropouts were found for entire 1 year of treatment duration, that is 100% adherence were observed in subjects undergoing treatment.

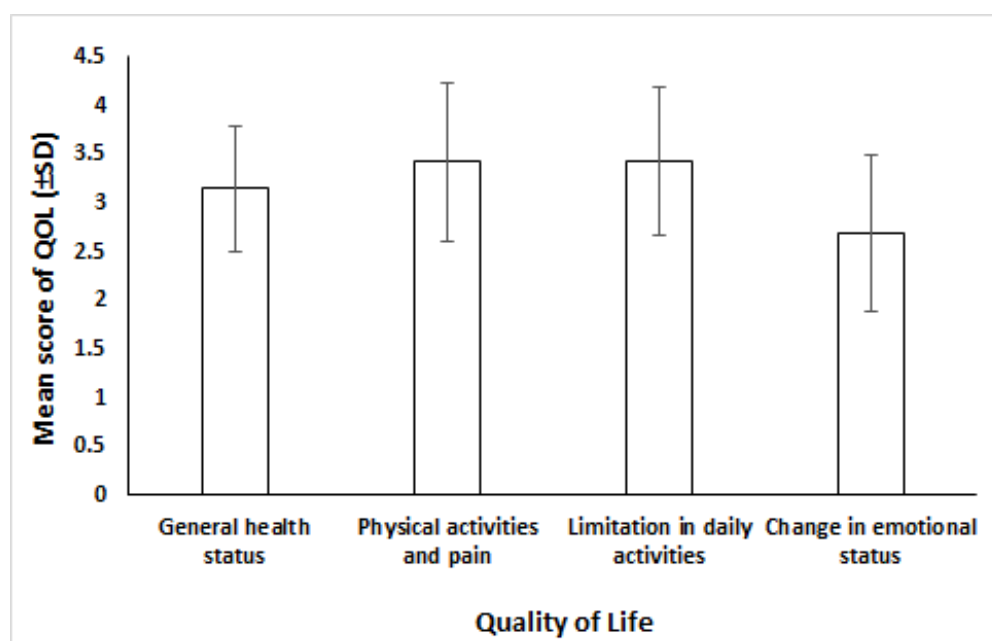


Figure 2: Mean score of Quality of Life in postmenopausal osteoporotic leprosy patients on once monthly Ibandronate after one year



## 4. Discussion

Development of osteoporosis in postmenopausal women is a well-established fact but its severity in general population and leprosy patients of postmenopausal age group may vary because of altered bony architecture and liable for frequent fractures. In this study, the participants falling within inclusion criteria were selected and were treated with Ibandronate once monthly for 1 year (Table 1).

There was significant change in BMD after 6 months and 12 months (Mean T-score -3.17, -2.89, -2.71. SD at baseline, at 6 months and at 12 months respectively) This confirmed that Ibandronate is highly effective in increasing BMD after one year of treatment (Table 2).

The research carried over indicates that treatment with Ibandronate increased hip BMD (14.51% after 12 months), Z-test with repeated measurements was used to examine the significance of the longitudinal changes in the BMD. Ibandronate reveals greater efficacy in increasing hip BMD through its effect to reduce remarkable bone turnover in postmenopausal leprosy patients with osteoporosis.

Ibandronate indicated more pronounced reduction in severity of osteoporosis in terms of Singh's index, which suggests that, there is improvement in quality of bone architecture. It has recently been established that the anti-fracture efficacy of anti-resorptive drugs cannot be explained simply by alterations of BMD, and that there is a need to assess the overall improvement of the bone quality in postmenopausal women with osteoporosis, when treated with these drugs [20,21]. Bone strength reflects both bone mass and bone quality, and bone quality is derived from bone architecture and turnover [22].

Clinically, the effects of the above-mentioned drug on severity of osteoporosis have not yet been clearly established. However, the Singh's index has poor reliability and poor diagnostic value in screening of femoral neck osteoporosis [23]. The incidence of fractures could be considered as an index of bone quality, because reduction of the fracture risk is considered to be the most convincing evidence of the improved bone quality. Increase of hip BMD, suggests that Ibandronate might have significant effect on bone quality.

Monthly regimen of Ibandronate confirmed having better tolerability and adherence in postmenopausal osteoporotic leprosy patients. 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 the findings; where majority of females in showed improvement in their QOL, with reference to physical activity and pain, limitations to daily activities, change in emotional status and general health status.

Thus, the present study might provide sufficient conclusion regarding the drug's effect on reducing severity of osteoporosis, with once monthly regimen in osteoporotic postmenopausal leprosy patients.

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