Efficacy of Teriparatide in Increasing Bone Mineral Density in Postmenopausal Women with Osteoporosis – An Indian Experience

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Abstract

Background and Objective: Osteoporosis is emerging as a leading cause of substantial morbidity in India, particularly in postmenopausal women. Teriparatide (recombinant human parathyroid hormone [1-34]) increases bone formation and improves bone microarchitecture, thereby reducing the risk of fractures. This study was conducted to evaluate the efficacy of teriparatide in increasing bone mineral density (BMD) in postmenopausal women with osteoporosis.

Material and Methods: A randomised, prospective, multicentre, open-label, controlled study was conducted on 82 postmenopausal women with established osteoporosis. Patients were randomly divided into control and teriparatide groups, each group consisting of 41 patients. All the patients were supplemented with 1000 mg of elemental calcium and 500 IU of vitamin D throughout the study period of 180 days. Besides, teriparatide group patients were administered teriparatide 20 µg daily subcutaneously. Lumbar spine, femoral neck and total hip BMD, bone mineral content (BMC) and bone area were measured by dual energy x-ray absorptiometry (DXA) at baseline and at the end of 6 months of treatment. Bone biomarkers, such as serum bone specific alkaline phosphatase (BSAP) and serum osteocalcin (OC), representing bone formation, and urinary deoxypyridinoline (DPD), representing bone resorption were assessed at baseline, and at 3 and 6 months of treatment.

Results: During the study period, 9 patients (11%) were lost to follow-up - 6 in control group (7.3%) and 3 in teriparatide group (3.7%). There was an excellent compliance to both oral and injectable medication. The investigational product teriparatide was well tolerated and there were no serious adverse events. In addition, there were no significant differences between the groups in the incidence of adverse events. The percentage of increase in lumbar spine BMD, which is the primary endpoint, was significantly (P<0.001) higher in teriparatide group compared to that in control group (6.58% vs. 1.06%). Further, teriparatide significantly increased percentage of change in lumbar spine T-score (P<0.001), BMC (P<0.001) and bone area (P<0.028) compared to control group at 6 months. Administration of teriparatide resulted in a significant percentage of increase in all the bone biomarkers in teriparatide group compared to control group patients at 3 and 6 months over baseline, thereby showing that there was a significant increase in bone turnover in teriparatide group of patients.

Conclusion: These results show that teriparatide is an effective and safe drug in increasing the BMD and therefore, teriparatide provides yet another new therapeutic option for reducing the risk management of osteoporosis in postmenopausal women (clinicaltrials.gov number, NCT00500409). ©

INTRODUCTION

Osteoporosis has now been recognised as a major public health problem associated with substantial morbidity and socio-economic burden. As a result of osteoporosis, one in two women and one in five men over the age of 50, sustain fractures.1 Postmenopausal women, in particular, are more vulnerable to osteoporosis. After menopause, due to lack of oestrogen, the rate of bone turnover increases, resulting in accelerated bone loss.
A recent study reports 29% prevalence of osteoporosis in 30-60 year age group Indian women.5

Majority of currently approved therapies for osteoporosis act by inhibition of bone resorption and remodelling. Despite their great value, use of these anti-resorptive agents generally leads to marginal increases in BMD from 1-8%, and fracture risk reduction from 30-50%.3,4 Parathyroid hormone (PTH) analogue, teriparatide (recombinant human PTH [1-34]), represents a new class of anabolic therapies for management of severe osteoporosis both in men and women.5,6 Teriparatide stimulates bone formation, increases bone mass, and improves microarchitecture. A large randomized, placebo-controlled trial of teriparatide reported dose-related increases in lumbar spine BMD of 9.7-13.7% after a median treatment of 21 months with a significant reduction in both incident vertebral (65-69%) and non-vertebral fractures (~53%).7

Ethnicity and race are well known determinants of skeletal health and bone mineral density. BMD values in Indian population are approximately 15% lower than those in Caucasian women.8,9 In addition, fractures are reported to occur 10 – 20 years earlier in Indians than in the western population.10 One of the reasons could be that majority of Indians have low vitamin D status and are on low dietary calcium which makes them prone to bone diseases.11 Keeping these factors in view, the present study was conducted to evaluate the efficacy and safety of teriparatide in Indian postmenopausal women with osteoporosis.

METHODS

Study design

An open-label, multicentre, prospective, randomised, controlled phase III study was conducted, with the approval of Drug Controller General of India, at 6 outpatient endocrinology clinical centres in India, from December 2005 to August 2007. The primary efficacy endpoint was the percentage of change at the end of 6 months over baseline in bone mineral density (BMD) at lumbar spine (L1-L4) in postmenopausal women with osteoporosis. The secondary efficacy endpoint was percentage of change from baseline in biomarkers of bone formation [serum bone specific alkaline phosphatase (BSAP) and serum osteocalcin (OC)], and bone resorption [urinary deoxypyridinoline (DPD)] at the end of 3 and 6 months. Study protocol was approved by the Ethics Committees of respective investigational centres.

Study Participants

Postmenopausal women, at least 3 years past menopause, were eligible to participate if they were aged between 45-75 years and had osteoporosis (lumbar spine or femoral neck or total hip T-score ≤-2.5). Women were excluded if they had vertebral abnormalities in L1-L4 that interfered with measurement by dual energy X-ray absorptiometry (DXA). Other exclusion criteria were: women with significant liver disease, gastrointestinal disease, renal insufficiency (serum creatinine >2.0 mg/dl) or kidney stones; abnormal thyroid function (serum TSH normal range 0.5-5.0 µIU/ml); vitamin D deficiency (serum 25-OH vitamin D <20 ng/ml); serum PTH > 65 pg/ml; history of cancer within last 10 years; women who had used any medications that were known to affect bone (oestrogen and oestrogen-related compounds, bisphosphonates, fluoride, or calcitonin) within the previous 6 months or currently taking systemic prednisone, inhaled steroids, anticoagulants and anticonvulsants. Written informed consent was obtained from all patients before they were enrolled into the study.

Treatment

Teriparatide used in the study was obtained by expression of the human PTH gene in Escherichia coli and was manufactured by Virchow Biotech. During screening, postmenopausal women, who consented to participate in the study, were supplemented with 1000 mg of elemental calcium and 500 IU of vitamin D for 45 days. Eligible patients were randomly assigned to either control group or teriparatide group in the ratio of 1:1 following the block randomisation list generated for each of the 6 investigating centres, with block sizes of 4. Besides 45 days of run-in phase period, all the patients received elemental calcium and vitamin D during the entire study period of 180 days; in addition, patients in teriparatide group received teriparatide 20 µg subcutaneously once a day. Compliance with the treatment was evaluated by tablet count of oral drug (1000 mg elemental calcium and 500 IU of vitamin D) and measurement of volume of injectable study material (teriparatide) returned at each visit.

DXA parameters

T-scores, BMD, bone area and BMC at the lumbar spine (L1-L4), total hip and femoral neck were measured by DXA at baseline and at six months, using either Hologic (n=52) or GE Lunar (n=30) densitometer. Same instrument at each centre was used for measurement at baseline and at 6 months.

Biochemical investigations

Blood and urine samples were collected at screening, baseline, 1, 3 and 6 months for haematological and biochemical parameters. Samples were stored at -80 °C until they were analysed centrally. Routine haematology tests were conducted at the predefined laboratories of the respective centres. Serum 25-OH vitamin D, serum PTH and serum TSH were assessed at screening. While radioimmunoassay was used for vitamin D estimation, chemiluminescence immunoassay was used for serum TSH and PTH. In addition serum calcium and creatinine, urinary calcium and creatinine were monitored at each visit. Serum bone specific alkaline phosphatase (BSAP), serum osteocalcin (OC) and urinary deoxypyridinoline
(DPD) were measured with ELISA using Metra Biosystems, Mountview, CA, USA at baseline, at 3 and 6 months.

**Adverse events**

Patients were questioned at each visit about any adverse events, including minor complaints regardless of association with the study medication.

**Statistical Analysis**

The primary endpoint for efficacy evaluation was change in lumbar spine BMD. Difference in lumbar spine BMD between control and teriparatide treated groups was reported to be 0.025 g/cm² with a standard deviation change of 0.036. Based on this, the number of subjects needed per treatment group was calculated using following assumptions: 5% level of significance, 80% power for two-sided test assuming 15% attrition rate. The calculated sample required was 39 patients in each arm.

The results of all women who received at least one dose after randomisation were included in the intent-to-treat analysis. Data on baseline characteristics were analysed for differences between control and teriparatide treated groups by using t-test for independent samples. All the statistical tests were performed at 0.05% (two-sided test) α-level. The primary criterion was percentage of change in lumbar spine BMD from baseline to 6 months. The differences in the percentage of change from baseline to 6 months between control and teriparatide treated groups in DXA parameters were tested by using non-parametric Wilcoxon - Mann - Whitney U test. The secondary criterion was percentage of change from baseline in biomarkers of bone formation and bone resorption at the end of 3 and 6 months. The differences in the percentage of change from baseline to 3 and 6 months between control and teriparatide treated groups in bone biomarkers were tested by using non-parametric Wilcoxon - Mann - Whitney U test. The differences in the percentage of change from baseline to 3 and 6 months between control and teriparatide treated groups were tested by using Z-test for proportions. All tests were performed with the use of SAS statistical software, version 8 (SAS Institute).

**RESULTS**

A total of 207 postmenopausal women with suspected osteoporosis were subjected to DXA screening at 6 investigational centres. Among them 91 failed in DXA and the remaining 116 postmenopausal women with osteoporosis (lumbar spine or total hip or femoral neck T score < -2.5) were supplemented with elemental calcium 1000 mg and vitamin D 500 IU daily. After 45 days, they were screened for their eligibility, and 82 women met the eligibility criteria. They were randomly assigned to either control group (n=41) or teriparatide group (n=41). Of a total of 82 patients, 73 patients (89%) completed the trial and only nine patients – 6 in control group and 3 in teriparatide group, were lost to follow-up (Fig. 1). There was no significant difference in number of patients lost to follow-up between the groups. Both oral and injectable medications were well tolerated and as a result, compliance with oral medication averaged 97.3% and 98.1% for the control group and teriparatide group respectively. Similarly compliance with injectable medication was 97.4% in teriparatide group.

The baseline characteristics of patients assigned to two groups are presented in Table 1. At baseline,
no significant differences between two groups were observed in demographic characteristics, DXA and biochemical parameters. Treatment with teriparatide resulted in a significant (P<0.001) increase in lumbar spine BMD at 6 months over baseline, which was the primary endpoint. The percentage of increase in lumbar spine BMD was 6-fold higher in teriparatide treated patients compared to that of control group (6.58 Vs. 1.06). Besides, there were also significant increases in lumbar spine T-score, bone area and BMC. In contrast to lumbar spine, teriparatide group did not result in significant changes in T-score, BMD, bone area and BMC at total hip and femoral neck (Table 2).

Teriparatide treatment produced a significant increase in all measured biochemical markers of bone formation (serum BSAP and serum OC) and bone resorption (urinary DPD) both at 3 and 6 months over baseline (Fig. 2).

Safety profile in the two study groups was similar, adverse events were reported in 9 patients both in control and teriparatide groups (Table 3). Though 11 adverse events were reported in control group and 18 in teriparatide group, these differences were not statistically significant. In addition, the incidence of specific adverse events was similar between the control and teriparatide groups. There were also no serious adverse events in any of the patients of control and teriparatide groups.

**DISCUSSION**

Osteoporosis is a major public health problem that will become more widespread as the population ages. Osteoporosis, being a risk factor for fracture, accounts for high morbidity and mortality, especially in the elderly. Postmenopausal women are highly susceptible to osteoporosis and its associated complications. In recent years, therefore, greater attention has been focused on the development of antiosteoporotic drugs.

As osteoporosis results due to imbalance in

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<th>Table 2: Percentage of change in DXA scores from baseline to 6 months</th>
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*p<0.001; **p<0.03; Values are mean ± SD

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<th>Table 3: Number of patients (%) with adverse events in control and teriparatide groups</th>
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Fig. 2: Mean percentage change in serum BSAP (A), osteocalcin (B) and urinary DPD (C) levels at 3 months and 6 months over baseline (*P<0.05; **P<0.01; ***P<0.02; ****P<0.001). Error bars indicate ± SE
bone formation and bone resorption, ideally, an antisteporotic drug should increase bone formation compared to bone resorption. Most current therapies for osteoporosis, including the bisphosphonates, hormone replacement therapy, selective oestrogen receptor modulators and calcitonin, act by reducing bone turnover. Since patients with osteoporosis have lost skeletal mass of more than 25% of the normal, even with treatment with these drugs, many patients continue to have a BMD that remains within the osteoporotic range, and many continue to have the risk to fracture.\(^{22}\) In contrast, anabolic agents such as teriparatide increase bone formation over bone resorption, and as a result, increase BMD, thereby reducing the fracture risks.\(^{13,14}\) Apart from differences in ethnicity, environmental factors such as low dietary calcium intake and widespread vitamin D deficiency, are known to affect skeletal health. Indeed, it is reported that BMD is approximately 15% lower and fractures occur 10–20 years earlier in Indians than in the western population.\(^{6,10}\) In view of these reasons, the current study has been undertaken to evaluate the efficacy and safety of teriparatide in Indian postmenopausal women.

The present study is a randomised, open-label, prospective, multicentre, controlled trial. Placebo-controlled studies are widely accepted as the ideal way of obtaining unbiased estimates of treatments. However, this trial is not a placebo-controlled study; both groups of patients were supplemented with calcium and vitamin D during the entire study period. In view of their historical value in efficacy evaluation, conducting placebo-controlled clinical trials are currently under debate. The World Medical Association has recently revised Declaration of Helsinki, condemning the use of placebo in studies when established therapies are available.\(^{15}\) Besides, the prevailing opinion is that new therapeutic agents should be evaluated in comparison to current treatments to demonstrate equivalence, non-inferiority or superiority.\(^{14}\) Long term studies, including Cochrane meta-analysis, showed a beneficial effect of supplementation of calcium and vitamin D in prevention of hip and non-vertebral fractures among elderly women.\(^{17}\) On the basis of these studies, the control group of patients were supplemented with calcium and vitamin D during the entire study period of 6 months instead of a placebo.

In the current study, 82 postmenopausal women with osteoporosis, who met the eligibility criteria, were randomly assigned to two groups – control group or teriparatide group. Both groups of patients had similar baseline demographic and biochemical characteristics as well as bone parameters as assessed by DXA, thereby confirming the effective application of randomised block design. Among the 82 patients randomised, 73 patients (89%) completed the study and only 9 patients (11%) were lost to follow-up – 6 patients (14.6%) in control group and 3 patients (7.3%) in teriparatide group. Compliance to medication was closely monitored throughout the study period. Not only was there an excellent compliance to oral medication comprising calcium and vitamin D supplementation (97.7%), there was also similar compliance to daily injections in teriparatide group of patients (97.4%), since the drug was well tolerated and there were minimal side effects.

After treatment for 6 months, there were no significant differences in absolute DXA scores (T-scores, BMD, BMC and bone area) between control and teriparatide group patients for any of the sites viz., lumbar spine, total hip and femoral neck (results not presented). The primary endpoint considered in this was the percentage of change in lumbar spine (L1-L4) BMD at 6 months over baseline. Teriparatide treatment for 6 months resulted in 6.58 ± 6.50% increase in lumbar spine BMD compared to 1.06 ± 4.81% increase in control group patients. This difference was highly significant (P<0.001). These results are in conformity with published studies.\(^{14,18,19}\) Since changes in BMD are related to 30-41% reduction in fracture risk,\(^{20}\) observed increase in lumbar spine BMD with osteoporosis is likely to result in reduced risk of vertebral fractures. In addition, teriparatide produced a significant change in lumbar spine T-score, BMC and bone area compared to that in control group of patients. However, there were no significant changes in total hip and femoral neck BMD between control and teriparatide treated patients. It has been shown that in lumbar spine, which is a predominantly trabecular bone, teriparatide acts differently from that of hip, which roughly contains equal amounts of cortical and trabecular bone.\(^{12}\) Disparate effects of teriparatide on trabecular and cortical bone may explain differences in its effects on lumbar and hip BMD.

Both BMD as well as biochemical markers of bone turnover have been used in clinical practice and in research in osteoporosis. Results of the study have shown that teriparatide treatment significantly increases all bone biomarkers of both bone formation (serum BSAP, serum OC) and resorption (urinary DPD) at 3 months and 6 months over baseline, thereby showing that administration of teriparatide significantly increased bone turnover. Recently, NIH Workshop evaluated the role of biomarkers as surrogate endpoints in clinical trials and concluded that the combined information from biomarkers and clinical outcomes provides strongest rationale for optimal use of interventions.\(^{21}\) In view of this, apart from changes in BMD which is a primary endpoint, information on percentage of change in biomarkers of bone formation and bone resorption at 3 months and 6 months over baseline was collected as secondary endpoint.

In this study, the efficacy of teriparatide in reducing the risk of vertebral fractures, which is considered as
a gold standard in the assessment of antosteoporotic drugs, has not been evaluated. In this context, it needs to be noted that even in high risk populations, fractures are too infrequent, and therefore, extremely large sample size would be required to detect meaningful differences between control and therapeutic agent treated groups, using fracture end points. In view of this, in a recent report, the Surgeon General of US also specifically recommended the value of BMD and bone biomarker measures as surrogates for fracture efficacy in clinical trials of therapeutic agents.22

Treatment with teriparatide for 6 months was safe and well tolerated. Only minor side effects such as headache, nausea, dizziness, leg cramps were reported. Despite the rigorous daily subcutaneous injection regimen, compliance was excellent. It has not produced any severe or serious adverse events. The frequency of adverse events and the number of patients with adverse events between control and teriparatide group were also not statistically different thereby showing that teriparatide is a safe drug for the treatment of osteoporosis. Often, hypercalcemia has been reported in a minority (about 10%) of patients during treatment with teriparatide. In such cases, reduction in calcium intake or teriparatide dose has been recommended. However, in the current study, none of the patients in the teriparatide group developed hypercalcemia, probably because of low calcium dietary intake which is common among Indians. As a result, there was no need to reduce the dose of teriparatide in any of the patients.

Majority of drugs currently available for the treatment of osteoporosis are based on reducing the resorption rather than increasing the formation of bone. Despite the availability of these drugs, many patients continue to fracture while on therapy either due to inadequate increase in BMD or are unable to tolerate the drugs.23,24 Therefore, there is a place in treatment armamentarium for the new bone formation agents such as teriparatide with proven efficacy. Available evidence shows that teriparatide increased BMD at most sites and decreased non-vertebral fractures more than antiresorptive drugs such as alendronate.14,25 Teriparatide being an anabolic drug, increases lumbar spine BMD, BMC, thereby showing that it would be an ideal drug for the treatment of osteoporosis. The only limitation of its use is that like insulin, it needs to be administered subcutaneously daily.

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