Original Article

An observational study to assess back pain in patients with severe osteoporosis treated with teriparatide versus antiresorptives: An Indian subpopulation analysis

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ABSTRACT

Background: One year, prospective, observational study in an Indian subpopulation to assess back pain in patients with severe osteoporosis treated with teriparatide or antiresorptives in a clinical setting. **Materials and Methods:** One hundred and nineteen teriparatide-naïve Indian men and postmenopausal women (mean age 68.0 years) with previous osteoporotic vertebral fracture participated. Patients were assessed at baseline, 6-and 12-months to evaluate relative risk (RR) of new/worsening back pain using the Back Pain Questionnaire. The incidence of back pain and changes in back pain severity were assessed using the visual analog scale (VAS); Health outcomes were assessed using the euroquol-5 dimensions (EQ-5D) questionnaire. All tests were conducted with a two-sided alpha of 0.05. **Results:** Of 562 overall patients, 57, 60, and 2 Indian patients received teriparatide, antiresorptive, or teriparatide and antiresorptive, respectively. Baseline disease characteristics were slightly worse for antiresorptive-treated patients, whereas teriparatide-treated patients were older with more comorbidities. At 6-months, the incidence of new/worsening back pain was 5.3% for teriparatide-treated patients versus 4.4% for antiresorptive-treated patients (RR: 1.00, 95% confidence interval: 0.68, 1.48); the incidence of severe back pain was 0% versus 12.5% ($P = 0.017$); in these treatment groups, respectively. Mean VAS change scores (mean ± standard deviation [SD]) were − 1.9 ± 1.73 versus − 1.4 ± 1.77, and mean EQ-5D change scores were 4.2 ± 27.20 versus 9.9 ± 26.23 at 6-months. At 6 months, more teriparatide-treated patients felt better (89% vs. 61%; $P = 0.001$) and were at least very satisfied with their treatment (30% vs. 9%; $P = 0.011$). **Conclusion:** Teriparatide-treated Indian patients had similar new/worsening back pain risk and minimal risk of severe back pain compared with antiresorptive-treated patients at 6-months.

Key words: Antiresorptives, back pain, fractures, osteoporosis, teriparatide

Introduction

Osteoporosis is a chronic skeletal disorder characterized by decreased bone density and changes in bone microarchitecture leading to increased skeletal fragility and risk of low-trauma fractures with associated complications eventually leading to reduced health-related quality of life.[1-3] Vertebral fracture

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is the most common fracture and prevalence increases with age. In addition, vertebral fractures have significant acute complications, such as back pain and functional limitations, and chronic complications, including severe back pain, kyphosis, height loss, and physical and psychological impairment.[4,5]

Indirect estimates in 2003 suggested that 26 million Indians suffer from osteoporosis, making India one of the largest affected countries in the world, with the numbers projected to increase to 36 million by 2013.[6] The incidence of osteoporosis is noticed at an average age of 50–60 years in the Indian population, and osteoporotic hip fractures occur even at an earlier age in the lower socioeconomic groups. These high numbers of osteoporosis and age at occurrence may be due to the widespread prevalence (ranging from 53% to 85%) of Vitamin D deficiency with low dietary calcium intake in the Indian population,[7,8] which contributes to poor bone health and osteoporosis.

Most importantly, even after the first fracture has occurred, there are effective osteoporotic treatments to decrease the risk of further fractures, as well as the risk of developing acute or chronic back pain or its intensity.[9] Antiresorptive agents increase bone mineral density (BMD) by suppressing bone resorption, in turn improving bone strength and preventing fractures.[10]

Teriparatide (human parathyroid hormone 1–34, of recombinant DNA origin), a bone anabolic agent, is approved for the treatment of osteoporosis. Teriparatide stimulates bone formation by increasing osteoblast number and inhibiting osteoblast apoptosis, leading to increased BMD, improved bone quality (i.e. restoring bone microarchitecture), and reduced risk of both vertebral and nonvertebral fractures.[9,11] In addition, teriparatide demonstrated a significantly lower incidence of new/worsened back pain when compared with alendronate.[9]

This article reports the subanalysis of the Indian population in an observational study conducted in a multi-ethnic population in patients with severe osteoporosis with back pain who were treated with teriparatide or antiresorptives.[12]

Materials and Methods

Study patients

This article describes the subanalysis results of the Indian subpopulation from a 1-year, prospective, observational study that compared changes in back pain among teriparatide-treated versus. antiresorptive-treated patients with severe osteoporosis in a routine clinical setting. Since this was a nonrandomized study, treatment pattern and treatment initiation or changes were solely at the discretion of the physician and the patient. Patients were enrolled at 58 centers in nine countries/provinces: Hong Kong, India, Korea, Malaysia, Mexico, Pakistan, Singapore, Taiwan, and Thailand. In India, the study was conducted in eight centers. In this article, East Asia includes China, Hong Kong, Taiwan, and Korea; other includes Malaysia, Singapore, Pakistan, and Thailand.

Patients were teriparatide-naïve men and postmenopausal women who had a previous vertebral osteoporotic fracture sustained at least 6 weeks before joining the study. Patients consented to participate in the study and release information regarding treatment. They also agreed to return for follow-up visits; in the opinion of the prescribing physician, they were eligible to receive the intended treatment and comply with all the recommendations stated in the relevant product information.[12] Patients were excluded if they were contraindicated according to the relevant product information in the country/province in which they were being treated or if they were simultaneously participating in a different study that included a treatment intervention and/or an investigational drug.[12]

The study was reviewed and approved by ethical review boards. All the study methods and procedures were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable local laws and regulations.

Outcome measures

Assessments were performed at baseline, 6 months, and 12 months. Medical evaluations for patients with severe osteoporosis were planned at approximately every 6 months due to the high risk of fractures. The primary study endpoint included evaluation of relative risk (RR) of new/worsening back pain for patients treated with teriparatide versus those treated with antiresorptives at 6 months as assessed by the Back Pain Questionnaire.[12] Patients were considered to have new/worsening back pain if their score on question 2 of the Back Pain Questionnaire was worse than their score at baseline. Patients with severe back pain at baseline were not included in this analysis since their pain was already of maximum severity.

Secondary effectiveness measures were the incidence of back pain and changes in back pain severity using a 10-point visual analog scale (VAS), where zero is "no pain" and 10 is "worst possible pain." Safety variables included the occurrence of serious and nonserious adverse events (AEs) and events considered possibly related to therapy by the investigator. One or more incidence of treatment-emergent nontraumatic osteoporotic fractures any time during the study was counted as an event (new fractures).[12]

Health-outcome evaluations included treatment adherence, discontinuation of treatment at 1-year, reasons for treatment discontinuation, treatment satisfaction, and changes in health-related quality of life using the 100-point scale EuroQol-5 Dimensions (EQ-5D) questionnaire instrument to measure self-reported health-related outcomes, where zero is "the worst health you can imagine" and 100 is "the best health you can imagine."[12]

Treatment persistence was determined by asking patients to report the date of their first dose and the approximate date of their last dose. Patients were also asked at each visit to estimate the number of days that they missed taking their prescribed treatment. Investigators evaluated both aspects of treatment compliance at 3 months and 9 months.[12]

Statistical analysis

Of 562 overall patients among nine countries, this report analyzed Indian patients who comprised the second largest population (n = 119) in the study, after Mexico (n = 185).

All tests were conducted with a two-sided alpha of 0.05. No adjustments were made for multiple comparisons. Patients who received teriparatide or antiresorptive treatment or both at any time during the study were included in the safety cohort. Patients who received teriparatide or antiresorptive treatment, but not both, at baseline were included in the monotherapy cohort and classified according to the treatment received at baseline.[12] For all statistical comparisons, only monotherapy groups were compared.

The covariates used in the comparisons and models were baseline value and propensity score. The propensity score method was used to adjust for baseline differences and selection bias. The propensity score for each patient was derived using logistic regression with selected baseline characteristics as independent variables (i.e. demographics, vitals, alcohol and tobacco use, exercise, type of insurance, education, and medical history, including fracture and baseline assessments of disease and back pain). Two patients whose propensity scores were in non-overlapping regions of the propensity score distributions were removed from any comparative analyses.

Relative risk of new/worsening back pain at 6 months was estimated using the modified Poisson regression model adjusted for baseline back pain severity and propensity scores. The point estimate and 95% confidence interval (CI) for the RR were presented.

In addition, because of the small subgroup size of Indian patients, the primary analyses of new/worsening back pain were performed for the overall study group and by geographic regions for comparisons. RRs (95% CI) were presented for the overall group and by geographic regions adjusted for covariates (country, baseline severity of back pain, and propensity score) using a Poisson regression model and unadjusted for covariates using 2 × 2 table; results were displayed in the Forest graphs [Supplementary Figures 1 and 2].

The severity of back pain at 6 months was compared using a generalized logit model adjusted for baseline back pain severity. Odds ratios (95% CI) were calculated using "none" as the reference category.

The incidence of any back pain during the first 6 months was defined as at least one report of back pain (minor, moderate, or severe) from baseline to 6 months. Similarly, the incidence of any back pain was defined as at least one report of back pain (minor, moderate, or severe) at any time during the study. The odds of experiencing any back pain postbaseline during the first 6 months and any time during the study were calculated using the generalized logit model adjusted for propensity score and baseline back pain severity. Odds ratios (95% CI) were calculated using "none" as the reference category.

Descriptive analyses of actual values and change from baseline of VAS back pain severity scores were provided. Change from baseline in back pain VAS score was analyzed using a mixed-model repeated measure with baseline value and propensity score as covariates and treatment cohort, time point, and treatment cohort-by-time point interaction as fixed effects and patient and error as random effects. Unstructured covariance matrix was used to model the within-patient errors.

Descriptive analyses of actual values and change from baseline of EQ-5D health state scores of quality of life were provided. Cohorts were compared with respect to change from baseline in EQ-5D health state scores using an analysis of covariance model with baseline value and propensity score as covariates and treatment cohort as fixed effects.

Treatment adherence and satisfaction, discontinuation rate, and reasons for discontinuation were also summarized using descriptive statistics. Treatment discontinuation by 1-year was analyzed using logistic regression with treatment and propensity score in the model. For safety, summaries were provided for common, serious, and nonserious treatment-emergent AEs, treatment discontinuation due to AEs, and nontraumatic osteoporotic fractures.

Results

Of the 562 patients who received treatment, 119 patients were of Indian descent (teriparatide: N =57, antiresorptive:

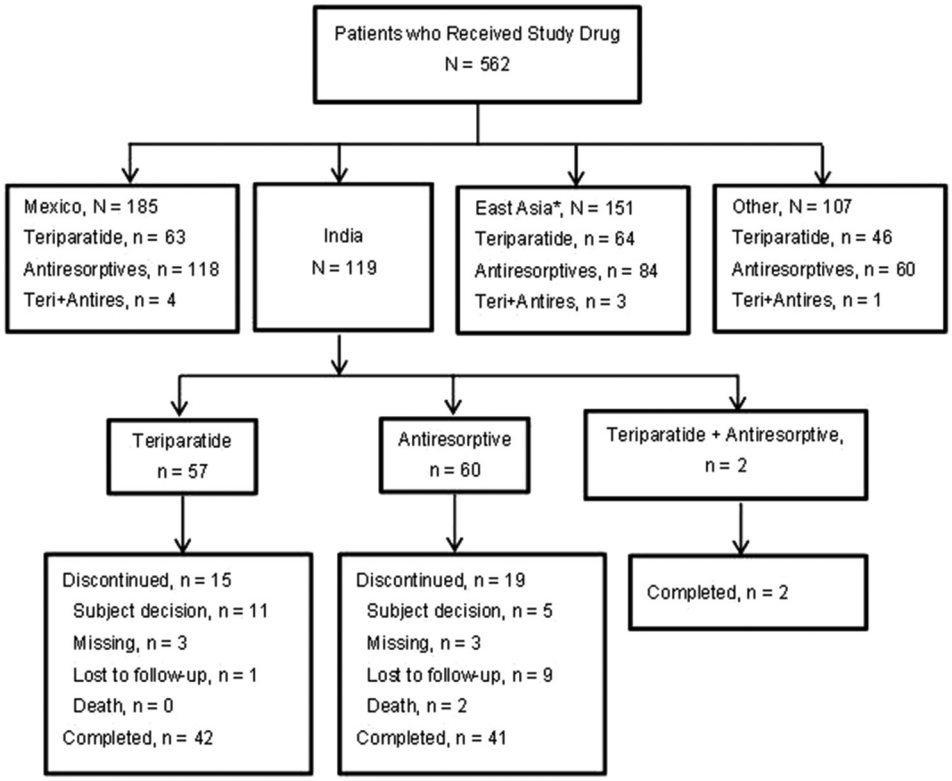

Figure 1: Patient disposition. N: Total number of patients, n: Number of patients in a specified category, Teri + Antires: Teriparatide and antiresorptive (*East Asia includes China, Taiwan, Hong Kong, and Korea; Other includes Malaysia, Singapore, Pakistan, and Thailand)

N =60, teriparatide and antiresorptive: *N* =2; Figure 1).[12] Among these Indian patients, 42 patients in the teriparatide group and 41 patients in the antiresorptive group completed the study. Fewer teriparatide-treated patients discontinued treatment than antiresorptive-treated patients (15 [26.3%] vs. 19 [31.7%] patients). The most common reason for discontinuation was "subject decision" (11 [19.3%] patients) in the teriparatide group and "lost to follow-up" (9 [15%] patients) in the antiresorptive group [Figure 1]. No statistically significant difference in treatment discontinuation by 1-year (adjusted for propensity score) was reported between the two groups (odds ratio: 1.12 [0.42, 3.01]; *P* = 0.815).

Patient demographics

Baseline demographics and disease characteristics were similar between the two groups with the exception of disease severity, which appeared to be worse for patients in the antiresorptive cohort compared to the teriparatide cohort [Tables 1a and 1b]. Furthermore, at baseline, the mean scores for VAS back pain severity and EQ-5D appeared to be worse in the antiresorptive group (5.8 and 48.0) compared with the teriparatide group (5.0 and 53.7) [Table 1c]. The mean age of patients was 66.1 years in the teriparatide group versus 62.5 years in the antiresorptive group. More patients in the teriparatide group had preexisting conditions compared with the antiresorptive group (hypertension: 36.8% vs. 16.7%, diabetes mellitus: 10.5% vs. 6.7%, hypothyroidism: 5.3% vs. 5.0%) [Table 1a].

Efficacy

For the primary endpoint, teriparatide-treated patients had a similar risk of new/worsening back pain as antiresorptive-treated patients at 6 months [Table 2]. The incidence of new/worsening back pain at 6 months was 5.3% for teriparatide-treated patients versus 4.4% for antiresorptive-treated patients (RR: 1.00; 95% CI: 0.68, 1.48). At 12 months, the incidence of new/worsening back pain was 0% versus 2.9% in the teriparatide and antiresorptive groups, respectively (RR: 0.99; 95% CI: 0.64, 1.55). Fewer teriparatide-treated patients had moderate back pain at 6 months compared to antiresorptive-treated patients; however, there was no significant difference between the two groups (31.8% vs. 42.9%; *P* = 0.303). At 12 months, significantly fewer teriparatide-treated patients had moderate back pain (6.1% vs. 24.4%; *P* = 0.036). At 6 months, no teriparatide-treated patients had severe back pain compared to seven patients on antiresorptive treatment (0% vs. 12.5%; *P* = 0.017). At 12 months, there was no significant difference between the two groups in terms of the occurrence of severe back pain (3.0% vs. 6.7%; *P* = 0.634) [Table 3]. The odds ratios (95% CI) of back pain severity at 6 months, using no back pain as a reference and adjusted for baseline back pain severity, were as follows:

Table 1 (a): Patient demographics and baseline characteristics-Indian population

Variable	Teriparatide (*N*=57)	Antiresorptive (*N*=60)	Teriparatide+Antiresorptive (*N*=2)
Age (years), mean (SD)			
Total	66.1 (10.56)	62.5 (10.67)	68.0 (1.41)
Female	66.4 (9.68)	62.6 (10.27)	69.0 (-)
Male	64.7 (14.15)	62.4 (12.83)	67.0 (-)
Gender, *n* (%)			
Female	46 (80.7)	49 (81.7)	1 (50.0)
Physical characteristics, mean (SD)			
Number of patients	56	60	2
Weight (kg)	57.1 (11.47)	60.3 (11.51)	62.5 (3.54)
Height (cm)	154.5 (9.82)	154.9 (9.38)	162.5 (9.19)
BMI (kg/m^2)	24.0 (4.64)	25.2 (4.67)	23.7 (1.34)
Osteoporosis medication, *n*			
No osteoporosis medication before study	56	60	2
Stopped before/at baseline	1	0	0
Alendronate sodium	1	0	0
Preexisting conditions occurring in >2% of teriparatide cohort, *n* (%)			
Hypertension	21 (36.8)	10 (16.7)	0 (0.0)
Diabetes mellitus	6 (10.5)	4 (6.7)	0 (0.0)
Hypothyroidism	3 (5.3)	3 (5.0)	0 (0.0)

BMI: Body mass index, *N*: Total number of patients, *n*: Number of patients in a specified category, SD: Standard deviation

Table 1 (b): Baseline Back Pain Questionnaire score- Indian population

Variable	Teriparatide (*N*=57)	Antiresorptive (*N*=60)	Teriparatide+Antiresorptive (*N*=2)
Any back pain in month prior to study entry, *n* (%)	49 (86.0)	60 (100.0)	2 (100.0)
Any back pain in 12 months prior to study entry, *n* (%)	49 (86.0)	60 (100.0)	2 (100.0)
Frequency of back pain in the last month			
Once or twice	1 (2.0)	4 (6.7)	0 (0.0)
A few times	11 (22.4)	2 (3.3)	0 (0.0)
Fairly often	9 (18.4)	11 (18.3)	0 (0.0)
Every day or almost every day	28 (57.1)	43 (71.7)	2 (100.0)
Severity of back pain in the last month			
Minor	3 (6.1)	9 (15.0)	0 (0.0)
Moderate	38 (77.6)	40 (66.7)	2 (100.0)
Severe	8 (16.3)	11 (18.3)	0 (0.0)
Extent to which activities were limited in the last month			
None	4 (8.2)	8 (13.3)	0 (0.0)
Minor	18 (36.7)	9 (15.0)	0 (0.0)
Moderate	21 (42.9)	28 (46.7)	2 (100.0)
Severe	6 (12.2)	15 (25.0)	0 (0.0)
Bed confinement in last month, days mean (SD)	3.1 (7.89)	4.9 (10.03)	15.0 (21.21)

N: Total number of patients, *n*: Number of patients in a specified category, SD: Standard deviation

0.35 (0.03, 4.02), minor; 0.19 (0.02, 2.35), moderate. Severe back pain was not estimated due to zero incidence in the teriparatide group. The odds ratios (95% CI) of any back pain during the first 6 months and anytime during study, no back pain as reference and adjusted for baseline back pain severity and propensity score, were as follows: 0.38 (0.08, 1.74) for any back pain during first 6 months and 0.38 (0.08, 1.75) for any back pain during the study.

Back pain severity measured using VAS improved significantly for both cohorts at 6 and 12 months [Table 4]; however, no significant treatment differences were noted at 6 and 12 months (95% CI at 6 months: -0.79, 0.72 and at 12 months: −0.61, 1.27).

The RR in the incidence of new/worsening back pain for teriparatide versus antiresorptive was similar in Indian patients when compared with patients across the geographic regions [Supplementary Table 1 and Supplementary Figure 1, covariates adjusted RR of new/worsening back pain (any, moderate/severe, severe) by geographic regions at 6 months]. The unadjusted RR in incidence of new/worsening back pain was numerically in favor of teriparatide in the Indian and Mexican populations and numerically in favor of antiresorptive's in the East Asian population [Supplementary Table 2 and Supplementary Figure 2, unadjusted RR of new/worsening back pain (any, moderate/severe, severe) by geographic regions at 6 months]. The difference in the incidence of new/worsening back

Table 1 (c): Baseline VAS and EQ-5D health state scores-monotherapy cohort–Indian population

Variable	Teriparatide (*N*=57)	Antiresorptive (*N*=60)	*P**
Back pain VAS, *n*	56	60	
Mean (SD)	5.0 (2.28)	5.8 (1.89)	0.067
EQ-5D health state score, *n*	56	60	
Mean (SD)	53.7 (21.85)	48.0 (21.88)	0.166
EQ-5D mobility, *n* (%)			0.757
No problems	18 (32.1)	16 (26.7)	
Some problems	35 (62.5)	39 (65.0)	
Confined to bed	3 (5.4)	5 (8.3)	
EQ-5D self-care, *n* (%)			0.953
No problems	37 (66.1)	38 (63.3)	
Some problems	16 (28.6)	18 (30.0)	
Unable to wash/dress self	3 (5.4)	4 (6.7)	
EQ-5D usual activities, *n* (%)			0.712
No problems	15 (26.8)	15 (25.0)	
Some problems	37 (66.1)	37 (61.7)	
Unable to perform usual activities	4 (7.1)	7 (11.7)	
EQ-5D pain/discomfort, *n* (%)			0.091
No pain/discomfort	4 (7.1)	2 (3.3)	
Moderate pain/discomfort	46 (82.1)	44 (73.3)	
Extreme pain/discomfort	5 (8.9)	14 (23.3)	
EQ-5D anxiety/depression, *n* (%)			0.211
No anxiety/depression	25 (44.6)	29 (48.3)	
Moderate anxiety/depression	29 (51.8)	24 (40.0)	
Extreme anxiety/depression	2 (3.6)	7 (11.7)	

**P* for continuous variable is based on *t*-test and for classification variable is based on Fisher's exact test. EQ-5D: European quality of life-5 dimensions questionnaire, *N*: Total number of patients, *n*: Number of patients in a specified category, SD: Standard deviation, VAS: Visual Analog scale

Table 2: Incidence of new/worsening back pain of patients- Indian population

Incidence of new/worsening back pain	*n* (%)		RR (95% CI)* (Poisson regression model with covariates)
	Teriparatide (*N*=49)	Antiresorptive (*N*=49)	
At 6 months, *n*	38	45	
Any	2 (5.3)	2 (4.4)	1.00 (0.68, 1.48)
Moderate/severe	1 (2.6)	2 (4.4)	1.01 (0.68, 1.48)
Severe	0 (0.0)	2 (4.4)	1.03 (0.70, 1.52)
At 12 months, *n*	29	34	
Any	0 (0.0)	1 (2.9)	0.99 (0.64, 1.55)
Moderate/severe	0 (0.0)	1 (2.9)	0.99 (0.64, 1.55)
Severe	0 (0.0)	0 (0.0)	NC

*Relative risk was calculated using Poisson regression model adjusting for baseline severity of back pain and propensity score. CI: Confidence interval, *N*: Total number of patients, *n*: Number of patients per specified category, NC: Not calculable, RR: Relative risk (of teriparatide over antiresorptive)

pain numerically favored teriparatide group in the Mexican population and favored antiresorptive group in the East Asian population [Supplementary Figure 3]. However, the differences between treatment groups were not significant.

The mean (standard deviation [SD]) number of days on therapy for the Indian subpopulation was 314.9 days (103.51) in the teriparatide group, 323.2 days (78.61) in the antiresorptive group, and 377.5 days (3.54) in the two patients who received both types of treatment.

Table 3: Severity of back pain at baseline, month 6 and month 12-monotherapy cohort- Indian population

Back pain	*n* (%)		*P**	*P*†
	Teriparatide (*N*=57)	Antiresorptive (*N*=60)		
At baseline, *n*	57	60	0.006	
None	8 (14.0)	0 (0.0)		0.002
Minor	3 (5.3)	9 (15.0)		0.127
Moderate	38 (66.7)	40 (66.7)		1.000
Severe	8 (14.0)	11 (18.3)		0.620
At 6 months, *n*	44	56	0.008	
None	5 (11.4)	1 (1.8)		0.084
Minor	25 (56.8)	24 (42.9)		0.227
Moderate	14 (31.8)	24 (42.9)		0.303
Severe	0 (0.0)	7 (12.5)		0.017
At 12 months, *n*	33	45	0.040	
None	6 (18.2)	2 (4.4)		0.065
Minor	24 (72.7)	29 (64.4)		0.472
Moderate	2 (6.1)	11 (24.4)		0.036
Severe	1 (3.0)	3 (6.7)		0.634

**P* is based on Fisher's exact test for association between category of back pain severity and treatment group per visit. †*P* is based on Fisher's exact test for comparing proportion of patients between treatment groups within each category of back pain severity per visit. *N*: Total number of patients, *n*: Number of patients per specified category

Safety

Overall, the number of serious adverse events (SAEs) was low in both treatment groups. The most common SAEs (≥2 events) were as follows: Antiresorptive group, death (n = 2). There were no reports of nontraumatic osteoporotic fractures or osteosarcoma in either treatment group. The incidence of treatment discontinuation due to AEs was 0% in the teriparatide group and 1.7% in the antiresorptive group [Table 5].

Quality of life

Health outcomes assessments were based on the EQ-5D [Table 6]. The mean ± SD EQ-5D health-state score at baseline was 53.7 ± 21.85 for the teriparatide group compared with 48.0 ± 21.88 for the antiresorptive group [Table 1c]. These scores improved significantly for both groups at 6 and 12 months [Table 6]. However, no significant differences between treatments were noted at 6 and 12 months (95% CI at 6 months: −10.59, 10.32 and at 12 months: −14.94, 5.82). A greater percentage of teriparatide-treated patients felt better compared to antiresorptive-treated patients in response to question 1 on the treatment satisfaction questionnaire ("How has treatment affected you?) at month 6 (89% vs. 61%; P = 0.001) and at month 12 (95% vs. 79%; P = 0.051) [Figure 2]. Similarly, for question 2 ("Please indicate how satisfied you are with medication you took during your participation in this study"), more teriparatide-treated patients were very satisfied with their treatment versus antiresorptive-treated patients at 6 months (30% vs. 9%) and at 12 months (49% vs. 30%) [Figure 2]. This difference was statistically significant at 6 months (P = 0.011) but not

Table 4: Change in back pain severity (VAS)-monotherapy cohort-Indian population

Back pain severity	Teriparatide (*N*=57)		Antiresorptive (*N*=60)		Treatment difference
	Actual	Change from baseline	Actual	Change from baseline	
At 6 months, *n*		46		54	
Mean (SD)	3.1 (2.32)	−1.9 (1.73)	4.3 (2.06)	−1.4 (1.77)	
Adjusted mean (95% CI)*		−1.65 (−2.16, −1.13)		−1.61 (−2.08, −1.14)	−0.04 (−0.79, 0.72)
At 12 months, *n*		38		43	
Mean (SD)	2.3 (2.44)	−2.5 (2.11)	3.0 (2.21)	−2.8 (2.37)	
Adjusted mean (95% CI)*		−2.50 (−3.15, −1.85)		−2.83 (−3.44, −2.23)	0.33 (−0.61, 1.27)

*Least-squares mean and 95% CI from mixed-model repeated-measures analysis were adjusted for baseline back pain VAS, country, and propensity score.
CI: Confidence interval, *N*: Total number of patients, *n*: Number of patients per specified category, SD: Standard deviation, VAS: Visual Analog scale

Table 5: Adverse event overview*-Indian population

Events	*n* (%)		Teriparatide+Antiresorptive (*N*=2) *n* (%)
	Teriparatide (*N*=57)	Antiresorptive (*N*=60)	
Deaths†	0 (0.0)	2 (3.3)	0 (0.0)
SAEs	3 (5.3)	2 (3.3)	0 (0.0)
Treatment discontinuations due to adverse events	0 (0.0)	1 (1.7)	0 (0.0)
TEAEs	5 (8.8)	3 (5.0)	0 (0.0)
Possibly related to study disease	1 (1.8)	0 (0.0)	0 (0.0)
Possibly related to adjunct treatment	1 (1.8)	0 (0.0)	0 (0.0)
Possibly related to concomitant therapy	1 (1.8)	0 (0.0)	0 (0.0)
Possibly related to another medical condition	3 (5.3)	0 (0.0)	0 (0.0)
Possibly related to study drug	1 (1.8)	1 (1.7)	0 (0.0)
Patients with ≥1 TEAE	5 (8.8)	3 (5.0)	0 (0.0)
Any nontraumatic osteoporosis fracture (baseline to month 6)	0 (0.0)	0 (0.0)	0 (0.0)
Any nontraumatic osteoporosis fracture (baseline to month 12)	0 (0.0)	0 (0.0)	0 (0.0)

*Patients may have been counted for >1 category, †Deaths were also included as SAEs; No death was assessed as related to study drug. *N*: Total number of patients, *n*: Number of patients per specified category, SAEs: Serious adverse events, TEAEs: Treatment-emergent adverse events

Table 6: EQ-5D questionnaire score-monotherapy cohort-Indian population

EQ-5D	Teriparatide (*N*=57)		Antiresorptive (*N*=60)		Treatment difference
	Actual	Change from baseline	Actual	Change from baseline	
At 6 months, *n*	47		55		
Mean (SD)	60.3 (24.15)	4.2 (27.20)	57.0 (20.85)	9.9 (26.23)	
Adjusted mean (95% CI)*		7.19 (0.11, 14.27)		7.33 (0.88, 13.77)	−0.14 (−10.59, 10.32)
At 12 months, n	39		43		
Mean (SD)	65.6 (20.65)	10.8 (21.14)	67.3 (19.76)	21.2 (31.92)	
Adjusted mean (95% CI)*		13.88 (6.87, 20.88)		18.44 (11.82, 25.06)	−4.56 (−14.94, 5.82)

*Least squares mean and 95% CI from analysis of covariance adjusted for baseline EQ-5D health state score, country, and propensity score. EQ-5D: European quality of life-5 dimensions, CI: Confidence interval, *N*: Total number of patients, *n*: Number of patients per specified category, SD: Standard deviation

statistically significant at 12 months ($P = 0.114$). For patients who had not discontinued study, treatment compliance in the teriparatide group was 95.9% at 6 months and 97.4% at 12 months and treatment compliance in the antiresorptive group was 100% at 6 and 12 months.

Discussion

The data reported here are an Indian subgroup analysis from a recently reported observational study conducted in multi-ethnic patients.[12]

In general, baseline disease characteristics in the Indian population were worse for the antiresorptive group compared with the teriparatide group. However, patients in the teriparatide group were older and had more associated comorbidities.[12]

Similar to the results for the Asian patients[12], teriparatide-treated Indian patients had a similar risk of new/worsening back pain as antiresorptive-treated patients at 6 months, and there was no significant difference observed for the VAS back pain severity and EQ-5D health state score at 6 and 12 months.

Back pain severity VAS in Indian patients improved significantly for both cohorts at 6 and at 12 months with no significant differences between treatment groups. However, in the overall population, at 12 months, there was a statistically significant improvement in back pain

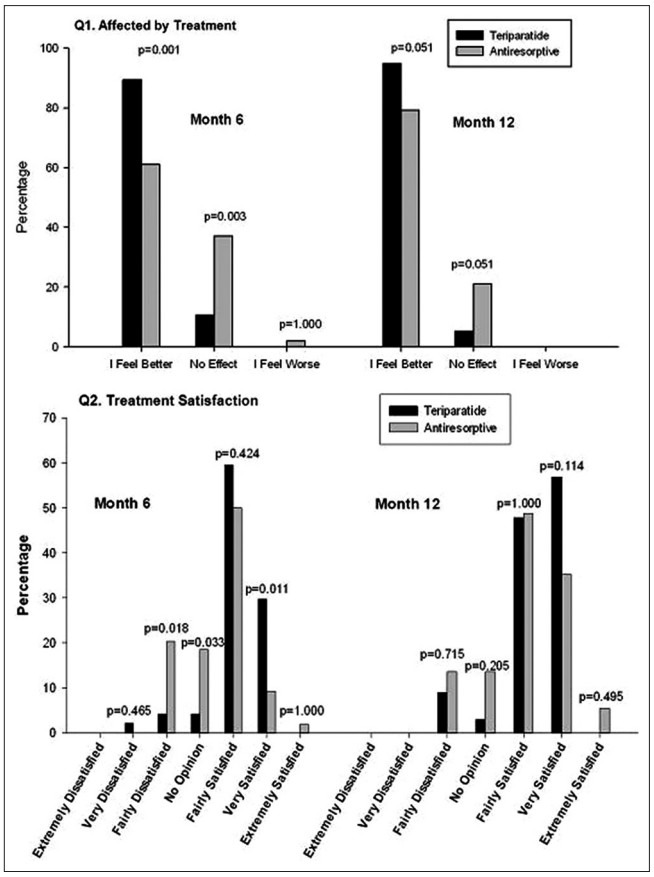

Figure 2: Health outcomes responses on treatment satisfaction questionnaire. Q1: Affected by treatment, Q2: Treatment satisfaction

severity in teriparatide-treated patients compared to antiresorptive-treated patients. The incidence of severe back pain at 6 months and moderate back pain at 12 months was significantly lower in the teriparatide group compared to the antiresorptive group. Significantly more teriparatide-treated patients felt better and were very satisfied with their treatment at 6 months. The results from the Indian subpopulation are consistent with the results reported in Caucasian patients with respect to health-related quality of life.[2]

The main strengths of this study are that the results apply generally since the sample represents the whole population, normal clinical practice settings of the study, and the longer duration of patient monitoring. The main limitation is the lack of randomization, which leads to selection biases like more associated comorbidities in the teriparatide group and the lack of assessment of back pain origin and its relatedness to osteoporosis.

Vertebral fractures are the most common type of fracture, accounting for 45% of osteoporotic fractures that lead to acute or chronic back pain.[5] Although these observational trial results are promising, more studies are needed on patients with back pain due to at least one moderate to severe vertebral fracture.

The results of this observational study in Indian ethnicity support previous findings with regards to effect on back pain during teriparatide treatment.[2,9,10]

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Conflict of interest

Sirel Gurbuz, Simrat Sohal, and Kyoungah See are employees of Eli Lilly and Company. The authors have no other direct or indirect commercial financial incentive associated with publishing the manuscript.

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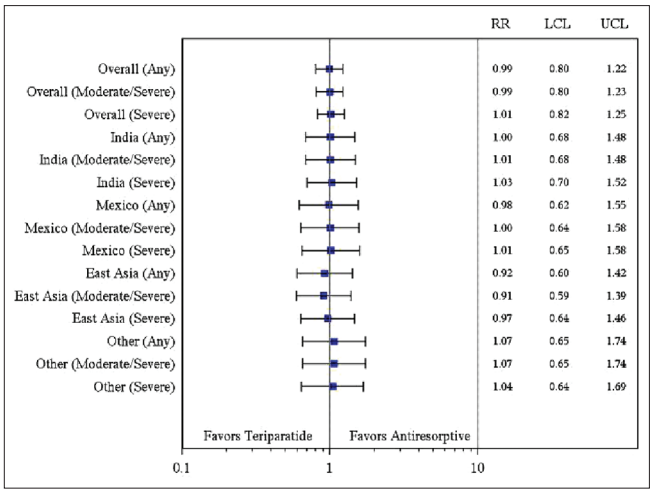
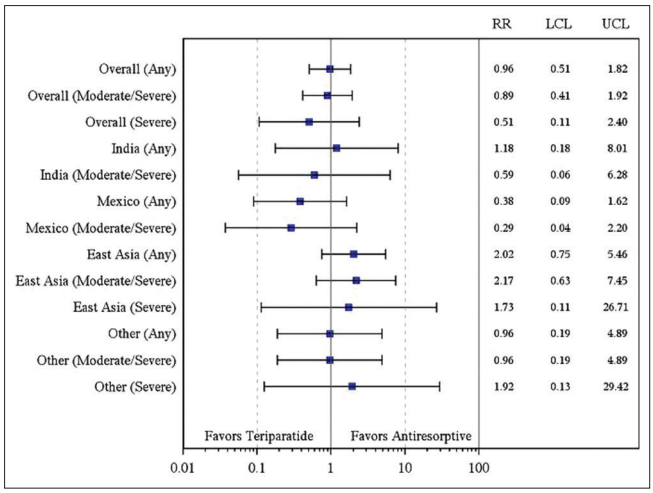
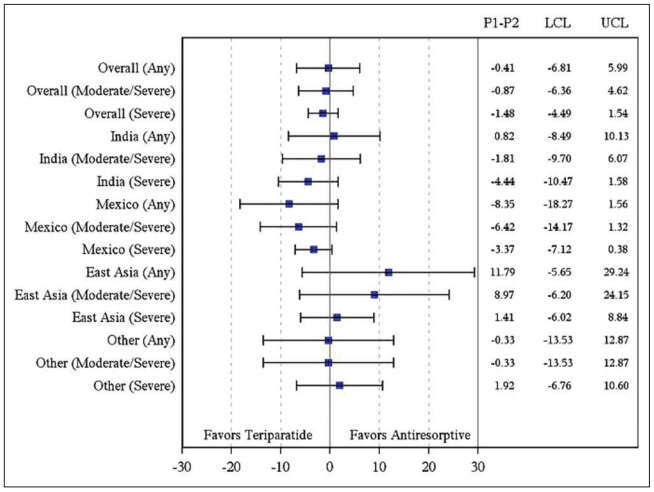


Supplementary Figure 1: Relative risk (95% confidence interval) of new/worsening back pain at 6 months by region (Poisson regression model with covariates). Relative risk was calculated by adjusting country, baseline severity of back pain, and propensity score. East Asia includes China, Hong Kong, Taiwan, and Korea; other includes Malaysia, Singapore, Pakistan, and Thailand



Supplementary Figure 2: Relative risk (95% confidence interval) of new/worsening back pain at 6 months by region (2 × 2 table). Relative risk was not adjusted for any covariate. East Asia included China, Hong Kong, Taiwan, and Korea; others included Malaysia, Singapore, Pakistan, and Thailand



Supplementary Figure 3: Difference in incidence rate (95% Confidence interval) of new/worsening back pain at 6 months by region (2 × 2 table). Patients with severe back pain at baseline were excluded. East Asia included China, Hong Kong, Taiwan, and Korea; Other included Malaysia, Singapore, Pakistan, and Thailand

Supplementary Table 1: Incidence of new/worsening back pain of patients at 6 months by region (poisson regression model with covariates)

Incidence of new/ worsening back pain	*n* (%)		RR (95% CI)* (poisson regression model with covariates)
	Teriparatide (*N*=159)	Antiresorptive (*N*=265)	
Overall	132	234	
Any	13 (9.8)	24 (10.3)	0.99 (0.80, 1.22)
Moderate/severe	9 (6.8)	18 (7.7)	0.99 (0.80, 1.23)
Severe	2 (1.5)	7 (3.0)	1.01 (0.82, 1.25)
India	38	45	
Any	2 (5.3)	2 (4.4)	1.00 (0.68, 1.48)
Moderate/severe	1 (2.6)	2 (4.4)	1.01 (0.68, 1.48)
Severe	0 (0.0)	2 (4.4)	1.03 (0.70, 1.52)
Mexico	39	89	
Any	2 (5.1)	12 (13.5)	0.98 (0.62, 1.55)
Moderate/severe	1 (2.6)	8 (9.0)	1.00 (0.64, 1.58)
Severe	0 (0.0)	3 (3.4)	1.01 (0.65, 1.58)
East Asia	30	52	
Any	7 (23.3)	6 (11.5)	0.92 (0.60, 1.42)
Moderate/severe	5 (16.7)	4 (7.7)	0.91 (0.59, 1.39)
Severe	1 (3.3)	1 (1.9)	0.97 (0.64, 1.46)
Other	25	48	
Any	2 (8.0)	4 (8.3)	1.07 (0.65, 1.74)
Moderate/severe	2 (8.0)	4 (8.3)	1.07 (0.65, 1.74)
Severe	1 (4.0)	1 (2.1)	1.04 (0.64, 1.69)

*Relative risk was calculated using poisson regression model adjusting for country, baseline severity of back pain and propensity score. East Asia includes China, Hong Kong, Taiwan, and Korea; Other includes Malaysia, Singapore, Pakistan, and Thailand. CI: Confidence interval, *N*: Total number of patients, *n*: Number of patients per specified category, RR: Relative risk (of teriparatide vs. antiresorptive)

Supplementary Table 2: Incidence of new/worsening back pain of patients at 6 months by region (2×2 table)

Incidence of new/ worsening back pain	*n* (%)		RR (95% CI)* (2×2 table)	Diff (95% CI)
	Teriparatide (*N*=159)	Antiresorptive (*N*=265)		
Overall	132	234		
Any	13 (9.8)	24 (10.3)	0.96 (0.51, 1.82)	−0.41 (−6.81, 5.99)
Moderate/severe	9 (6.8)	18 (7.7)	0.89 (0.41, 1.92)	−0.87 (−6.36, 4.62)
Severe	2 (1.5)	7 (3.0)	0.51 (0.11, 2.40)	−1.48 (−4.49, 1.54)
India	38	45		
Any	2 (5.3)	2 (4.4)	1.18 (0.18, 8.01)	0.82 (−8.49, 10.13)
Moderate/severe	1 (2.6)	2 (4.4)	0.59 (0.06, 6.28)	−1.81 (−9.70, 6.07)
Severe	0 (0.0)	2 (4.4)	0 (NC, NC)	−4.44 (−10.47, 1.58)
Mexico	39	89		
Any	2 (5.1)	12 (13.5)	0.38 (0.09, 1.62)	−8.35 (−18.27, 1.56)
Moderate/severe	1 (2.6)	8 (9.0)	0.29 (0.04, 2.20)	−6.42 (−14.17, 1.32)
Severe	0 (0.0)	3 (3.4)	0 (NC, NC)	−3.37 (−7.12, 0.38)
East Asia	30	52		
Any	7 (23.3)	6 (11.5)	2.02 (0.75, 5.46)	11.79 (−5.65, 29.24)
Moderate/severe	5 (16.7)	4 (7.7)	2.17 (0.63, 7.45)	8.97 (−6.20, 24.15)
Severe	1 (3.3)	1 (1.9)	1.73 (0.11, 26.71)	1.41 (−6.02, 8.84)
Other	25	48		
Any	2 (8.0)	4 (8.3)	0.96 (0.19, 4.89)	−0.33 (−13.53, 12.87)
Moderate/severe	2 (8.0)	4 (8.3)	0.96 (0.19, 4.89)	−0.33 (−13.53, 12.87)
Severe	1 (4.0)	1 (2.1)	1.92 (0.13, 29.42)	1.92 (−6.76, 10.60)

*Relative risk was not adjusted for any covariate and calculated as p1/p2 from 2×2 table. East Asia includes China, Hong Kong, Taiwan, and Korea; Other includes Malaysia, Singapore, Pakistan, and Thailand. CI: Confidence interval, *N*: Total number of patients, *n*: Number of patients per specified category, NC: Not calculable, RR: Relative risk (of teriparatide vs. antiresorptive), Diff: Difference of incidence (teriparatide vs. antiresorptive)