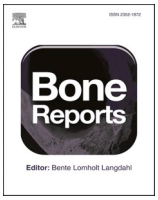
Bone Reports 18 (2023) 101689

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr



Changes in BMD T-score from pre-to post-treatment with biosimilar teriparatide: A single-arm, multi-center study

Mohsen G. Soroush [a], Maryam Kheirandish [b], Soosan Soroosh [a,*]

[a] Rheumatology Unit, AJA University of Medical Sciences, Tehran, Iran
[b] Department of Internal Medicine, Shahid Beheshti Hospital, Mazandaran University of Medical Sciences, Noshahr, Iran

ARTICLE INFO

Keywords:
Teriparatide
Osteoporosis
Bone mineral density

ABSTRACT

Introduction: Teriparatide is a recombinant analog of the parathyroid hormone and an anabolic treatment modality for osteoporosis. This study aimed to evaluate the effectiveness of biosimilar teriparatide (CinnoPar®, CinnaGen Co., Iran) in osteoporotic patients after at least one year of treatment.

Methods: In this multi-center, single-arm study, 239 eligible patients received subcutaneous injections of biosimilar teriparatide 20 μg once daily for at least one year. The main outcome measure was the change in bone mineral density (BMD) T-score from baseline (pre-treatment) to end of the study (post-treatment). In addition, the change in the fracture risk assessment tool (FRAX) score was calculated to estimate the 10-year probability of major and hip fractures pre-and post-treatment.

Results: A total of 239 patients (age, 63 ± 12.14 years; female, 88.28 %) were included, of which 27.62 % (66/239), 14.64 % (35/239), and 57.74 % (138/239) received biosimilar teriparatide for 12–16 months, 17–20 months, and 21–24 months, respectively. From baseline to end of the study, the T-score at the lumbar spine increased from −2.67 ± 1.04 to −2.26 ± 1.11 (mean percent change, 13.07 ± 62.89; p-value<0.001). Similarly, the T-score at femoral neck increased from −2.18 ± 0.87 to −2.09 ± 0.93 (mean percent change, 3.81 ± 31.52; p-value = 0.006). The proportions of patients with maintained or improved BMD T-score at the lumbar spine and femoral neck sites were 85.36 % (204/239) and 69.04 % (165/239), respectively. Similar results were obtained in subgroups of patients with rheumatoid arthritis and those with a history of a previous fracture or parental hip fracture. FRAX scores did not change significantly during the study (p-values of 0.551 and 0.973 at the lumbar spine and femoral neck, respectively).

Conclusion: We observed considerable improvements in BMD following treatment with the biosimilar teriparatide for one year or more. The biosimilar teriparatide can be considered as an effective treatment option in female and male patients with osteoporosis.

1. Introduction

Osteoporosis is a common disease with a large and growing social and economic burden on patients and health systems. This chronic disorder is characterized by a systemic reduction in bone mass and strength and changes in bone microarchitecture (Hernlund et al., 2013). Operationally, osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density (BMD) of 2.5 standard deviations (SDs) or more below the average value for healthy young female adults. BMD measured by dual x-ray absorptiometry (DXA) is widely used to diagnose osteoporosis and should be evaluated before the pharmacologic treatment of patients. Osteoporosis increases the risk of fragility fractures in patients and causes life-threatening complications in older adults. According to a WHO report, the lifetime risk for a wrist, hip, or vertebral fracture is estimated to be up to 40 % in patients with osteoporosis (Rohrbasser et al., 2018). Osteoporosis patients with spine and hip fractures experience considerable reductions in quality of life and have increased mortality rates (Rachner et al., 2011). The incidence of osteoporotic fractures in Iran is on the rise, which is putting a significant strain on both the healthcare system and the economy. Experts predict

Abbreviations: BMD, bone mineral density; FRAX, fracture risk assessment tool; SDs, standard deviations; DXA, dual x-ray absorptiometry; WHO, world health organization; PTH, parathyroid hormone; FDA, United States Food and Drug Administration; RRR, relative risk reduction; EQ-5D, EuroQol-5D; VAS, visual analog scale; QALYs, quality-adjusted life years; WTP, willingness-to-pay; GDP, gross domestic product.

* Corresponding author at: AJA University of Medical Sciences, Etemadzadeh Street, West Dr. Fatemi Street, Tehran 1411718541, Iran.
E-mail address: Soroosh44@yahoo.com (S. Soroosh).

https://doi.org/10.1016/j.bonr.2023.101689
Received 29 January 2023; Received in revised form 21 May 2023; Accepted 23 May 2023
Available online 25 May 2023

that there could be as many as 154,530 cases of osteoporotic fractures in Iran in 2020, leading to 3554 deaths. This alarming trend highlights the urgent need for increased awareness and preventative measures. The economic impact of osteoporosis in Iran is also considerable, with an estimated cost of 393.24 million US dollars. Since the originator's brand of teriparatide (Forteo®) is not widely available in Iran and considering the 24 months duration of therapy of this drug in the routine practice in Iran, this financial burden affects not only the healthcare system but also the overall economy. Therefore, it's crucial to identify effective strategies for preventing and treating osteoporosis to reduce its incidence in Iran (Ostovar et al., 2022).

Available osteoporosis therapies include antiresorptive agents, such as bisphosphonates, denosumab, and selective estrogen receptor modulators, and anabolic agents, such as parathyroid hormone (PTH), PTH-related protein analogs, and romosozumab. Antiresorptive agents and anabolic agents protect against osteoporosis by preventing bone resorption and increasing bone formation, respectively (Lim and Bolster, 2015; Tu et al., 2018).

Teriparatide is a 34-amino-acid recombinant analog of the human PTH and the first anabolic medication approved by the United States Food and Drug Administration (FDA) for the treatment of osteoporosis. It contains a sequence identical to the biologically active region (N-terminal portion) of PTH. Thus, teriparatide can mimic the physiological actions of PTH, including the regulation of bone metabolism and increasing renal calcium reabsorption and gastrointestinal calcium absorption (Pepe et al., 2020). In the treatment of postmenopausal women with osteoporosis (Chen et al., 2006), the combination of teriparatide with vitamin D and calcium resulted in a significant reduction in the risk of new vertebral fractures ($p < 0.001$; relative risk reduction (RRR), 65 %) and new non-vertebral fractures ($p < 0.05$; RRR, 53 %), compared with vitamin D and calcium alone. Also, the BMD at the lumbar spine and femoral neck significantly improved with teriparatide in postmenopausal women with osteoporosis. Similarly, in men with primary or hypogonadal osteoporosis (Orwoll et al., 2003) and patients with glucocorticoid-induced osteoporosis (Saag et al., 2009), treatment with teriparatide significantly increased the lumbar spine and femoral neck BMDs from baseline to endpoint of the studies. Currently, teriparatide is approved in the United States for the treatment of postmenopausal women with osteoporosis, men with primary or hypogonadal osteoporosis, and men and women with osteoporosis associated with chronic use of systemic glucocorticoids (prednisone 5 mg or more per day or an equivalent glucocorticoid), in patients who are at high risk for fracture or who have failed or are intolerant to other osteoporosis therapies (Pepe et al., 2020).

CinnoPar® is an Iranian biosimilar of recombinant human parathyroid hormone, produced from a strain of *Escherichia coli* bacteria, which has undergone genetic changes in this strain by recombinant DNA technology.

Biosimilars are imitations of already licensed biological products with similar quality, safety, and efficacy characteristics. Studies have shown that macroeconomic conditions are considerable barriers to timely patient access to biologic treatments. The introduction of comparably low-cost biosimilar agents can improve access to biologic therapies for eligible patients, particularly in low-income countries (Baumgart et al., 2019). However, adequate experimental and real-world clinical data is required to ensure healthcare providers that biosimilars are safe and effective agents while having the potential to reduce biologic treatment costs. A phase III randomized double-blind controlled trial previously reported the comparable efficacy and safety profiles of the biosimilar teriparatide (CinnoPar®, CinnaGen Co., Iran) compared to the innovator teriparatide (Forteo®, Eli Lilly and Company, USA) in 104 osteoporotic postmenopausal women after six months of treatment (Tabatabaei-Malazy et al., 2018).

In the current study, we aimed to evaluate the effectiveness of biosimilar teriparatide (CinnoPar®, CinnaGen Co., Iran) in osteoporotic patients after at least one year of treatment.

2. Material and methods

2.1. Study design

This was multi-center, single-arm study. Patients were recruited between November 2016 and June 2019. Verbal consent was obtained for all patients. The study was performed in line with the principles of the Declaration of Helsinki. The ethics committee of the local institutional review board and research of AJA University of Medical Sciences (IR.AJAUMS.REC.1398.236) approved the study.

Eligible participants were postmenopausal women or men with osteoporosis and a T-score of −2.5 or less with a prior fracture or a T-score of −3.0 or less without prior fracture at the lumbar spine or femoral neck; men with primary or hypogonadal osteoporosis; men and women with osteoporosis associated with chronic use of systemic glucocorticoids with a high risk of fragility fractures. Exclusion criteria were hypersensitivity to teriparatide or any component of the formulation, hypercalcemia defined as total calcium of >10 mg/dL, hypercalciuria defined as urinary calcium (mg/dL) to urinary creatinine (mg/dL), ratio of more than one, history of severe renal or hepatic impairment, recurrent nephrolithiasis, and treatment with PTH or strontium ranelate within six months prior to study entry.

2.2. Study interventions

All study patients received subcutaneous injections of biosimilar teriparatide (CinnoPar®, CinnaGen Co., Iran) 20 μg once daily for at least one year based on the physician's routine practice. Before prescribing teriparatide, bone density test and necessary tests were performed. Demographic characteristics of patients including age, weight, height, bone density and T-score in lumbar vertebrae and femur bone were investigated and recorded. All patients were advised to do appropriate exercises such as walking (at least 3 times a week and for 30 min each time), eating foods rich in calcium and stopping smoking. In case of insufficient or deficient levels of vitamin D, appropriate treatment was prescribed for the patients before the treatment.

2.3. Study outcomes

The objective of this study was to evaluate the effectiveness of biosimilar teriparatide in adults with osteoporosis. We measured pre-treatment and post-treatment BMD using DXA and reported the scan results as T-scores. All patients have been assessed at two centers by one central technician and identical “hologic discovery” Machines.

In addition, we used the WHO fracture risk assessment tool (FRAX) to calculate the absolute 10-year risk for major and hip fractures in recruited patients with all required data available (Leslie et al., 2011). This risk was assessed based on the geographic region of Iran and the patient surveys (https://frax.shef.ac.uk/frax/).

2.4. Statistical analysis

Descriptive statistics were reported as mean and standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Two-sided p-values were considered in all analyses. First, after refining the data, normality was checked using the Shapiro-Wilk test and it was determined that the condition of normality was met, then the paired *t*-test was used. Comparisons of categorized variables were conducted using Pearson's chi-squared test. All statistical analyses were performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). p values <0.05 were considered statistically significant.

3. Results

A total of 327 patients with osteoporosis or at risk for osteoporosis were screened for eligibility, and 239 were included in the study. 88

patients were excluded from the study for these reasons: hypercalcemia defined as total calcium of >10 mg/dL; hypercalciuria defined as urinary calcium (mg/dL) to urinary creatinine (mg/dL) ratio of more than one; history of severe renal or hepatic impairment; history of recurrent nephrolithiasis; treatment with PTH or strontium ranelate within six months prior to study entry. Some patients were not able to buy the drug due to its high price and no insurance coverage.

Baseline demographic and clinical characteristics are presented in Table 1. Most patients were female (88.28 %, 211/239) and at least overweight (body mass index of 25 or more; 68.6 %, 164/239). Of 211 female participants, almost all were post-menopause (98.10 %, 207/211), and 15.17 % (32/211) experienced premature menopause. Rheumatoid arthritis (13.81 %, 33/239), hypertension (14.64 %, 35/239), diabetes mellitus (7.11 %, 17/239), dyslipidemia (8.37 %, 20/239), and ischemic heart disease (4.60 %, 11/239) were the most common chronic health conditions other than osteoporosis among study participants. At study initiation, 35 patients (14.64 %) were on corticosteroid treatment (at least 5 mg prednisone daily or equivalent dose of other corticosteroids for at least 3 months). Fifty-six patients (23.43 %) reported a history of bisphosphonate use (They all received alendronate sodium, 70 mg weekly). Of 101 patients with available data, 31.68 % (32/101) reported a history of a previous fracture, and 7.92 % (8/101) reported a history of parental hip fracture.

Of 239 study participants, 78.24 % (187/239), 14.64 % (35/239), and 7.11 % (17/239) experienced an increase, a decrease, and no change in spine T-score from baseline to end of the study. The mean percent change in spine T-score was 13.07 ± 62.89 (from −2.67 ± 1.04 to −2.26 ± 1.11; mean change, 0.41 ± 0.54; p-value<0.001). Of 239 study participants, 47.28 % (113/239), 30.96 % (74/239), and 21.76 % (52/239) experienced an increase, a decrease, and no change in femoral neck T-score from baseline to end of the study. The mean percent change in femoral neck T-score was 3.81 ± 31.52 (from −2.18 ± 0.87 to −2.09 ± 0.93; mean change, 0.09 ± 0.49; p-value = 0.006).

Table 1
Demographic and baseline clinical characteristics of study patients.

Variable	Male patients (N = 28)	Female patients (N = 211)	Total (N = 239)
Age, years			
Mean ± SD	53.67 ± 15.44	64.23 ± 11.11	63 ± 12.14
Weight, kg			
Mean ± SD	71.96 ± 14.90	66.72 ± 12.22	67.34 ± 12.64
Height, cm			
Mean ± SD	169.53 ± 7.63	154.85 ± 7.35	156.57 ± 8.76
BMI, kg/m^2			
Mean ± SD	24.98 ± 4.63	27.85 ± 4.92	27.52 ± 4.96
n (%)			
<18.5	2 (7.14)	2 (0.95)	4 (1.64)
18.5–24.9	14 (50.00)	57 (27.01)	71 (29.71)
25–29.9	7 (25.00)	88 (41.71)	95 (39.75)
30–34.9	4 (14.29)	49 (23.22)	53 (22.18)
35–39.9	1 (3.57)	13 (6.16)	14 (5.86)
>40	0 (0)	2 (0.95)	2 (0.84)
Spine T-score			
Mean ± SD	−2.47 ± 0.93	−2.70 ± 1.05	−2.67 ± 1.04
n (%)			
≥−1	2 (7.14)	13 (6.16)	15 (6.28)
−1.1 to −2.5	12 (42.86)	75 (35.55)	87 (36.40)
<−2.5	14 (50.00)	123 (58.29)	137 (57.32)
Total	28 (100)	211 (100)	239 (100)
Femoral neck T-score			
Mean ± SD	−1.53 ± 0.69	−2.27 ± 0.85	−2.18 ± 0.87
n (%)			
≥−1	8 (28.57)	16 (7.58)	24 (10.04)
−1.1 to −2.5	20 (71.43)	120 (56.87)	140 (58.58)
<−2.5	0 (0)	75 (35.55)	75 (31.38)
Total	28 (100)	211 (100)	239 (100)

Of 239 study participants, 27.62 % (66/239), 14.64 % (35/239), and 57.74 % (138/239) received teriparatide treatment for 12–16 months, 17–20 months, and 21–24 months, respectively. There was no significant difference in the distribution of patients with improved, stable, or decreased T-scores at either the lumbar spine or femoral neck sites between patients grouped by the duration of teriparatide treatment (p-values of 0.780 and 0.808, respectively) (Fig. 1).

FRAX was calculated in 101 study participants. Based on this tool, the risk of major fractures (from 13.30 ± 10.15 to 13.58 ± 11.09; mean change, 0.28 ± 4.76; p-value = 0.551) and hip fractures (from 6.12 ± 6.85 to 6.11 ± 6.99; mean change, −0.01 ± 3.95; p-value = 0.973) did not change significantly from baseline to end of the study.

Of 33 patients with rheumatoid arthritis, 78.79 % (26/33), 18.18 % (6/33), and 3.03 % (1/33) experienced an increase, a decrease, and no change in spine T-score from baseline to end of the study. The mean percent change in spine T-score was 8.51 ± 34.61 (from −2.65 ± 0.97 to −2.31 ± 1.02; mean change, 0.34 ± 0.65; p-value = 0.005). Of these 33 patients, 63.64 % (21/33), 24.24 % (8/33), and 12.12 % (4/33) experienced an increase, a decrease, and no change in femoral neck T-score from baseline to end of the study. The mean percent change in femoral neck T-score was 2.64 ± 15.39 (from −2.46 ± 0.74 to −2.39 ± 0.76; mean change, 0.07 ± 0.32; p-value = 0.251).

Of 32 patients with a history of a previous fracture, 71.88 % (23/32), 25.00 % (8/32), and 3.13 % (1/32) experienced an increase, a decrease, and no change in spine T-score from baseline to end of the study. Of these 32 patients, 50.00 % (16/32), 34.38 % (11/32), and 15.63 % (5/32) experienced an increase, a decrease, and no change in femoral neck T-score from baseline to end of the study.

Of eight patients with a history of parental hip fracture, 62.50 % (5/8), 25.00 % (2/8), and 12.50 % (1/8) experienced an increase, a decrease, and no change in spine T-score from baseline to end of the study. Of these eight patients, 62.50 % (5/8), 37.50 % (3/8), and 0.00 % (0/8) experienced an increase, a decrease, and no change in femoral neck T-score from baseline to end of the study.

4. Discussion

In this single-arm, multi-center study, we evaluated the effectiveness of treatment with the biosimilar teriparatide by comparing the pre-intervention and the post-intervention BMD at the lumbar spine and femoral neck in 239 patients. We found that this biosimilar agent is a viable treatment option in female and male patients with osteoporosis. Treatment with biosimilar teriparatide either maintained or improved the BMD at the lumbar spine and femoral neck in considerable proportions of patients (85.36 % and 69.04 %, respectively). Similar improvement rates were also found in the subgroups of patients with rheumatoid arthritis, a history of a previous fracture, and a history of parental hip fracture.

The lumbar spine BMD is generally considered the best site for assessing treatment-related effects in the management of osteoporosis (Sheu and Diamond, 2022). In our study, the mean percent changes of lumbar spine and femoral neck T-score were 13.07 % (p-value < 0.001) and 3.81 % (p-value = 0.006) from baseline to endpoint, respectively. Similarly, in an 18-month prospective cohort study, Panico et al. (2011) reported increases of 12.4 % and 5.2 % with teriparatide 20 μg/day (42 postmenopausal women) compared with increases of 3.85 % and 1.99 % with alendronate 70 mg/week (39 postmenopausal women) in BMD at the lumbar spine and femur, respectively. In a 78-week randomized controlled trial, Malouf-Sierra et al. (2017) showed superior efficacy of teriparatide 20 μg/day (86 patients) over risedronate 35 mg/week (85 patients). They reported increases of 11.08 % and 1.96 % with teriparatide compared with changes of 6.45 % and −1.19 % with risedronate in BMD at the lumbar spine and femoral neck, respectively.

It is generally recommended to initiate BMD follow-up testing at least one year after a change in osteoporosis treatment (Small, 2005). In

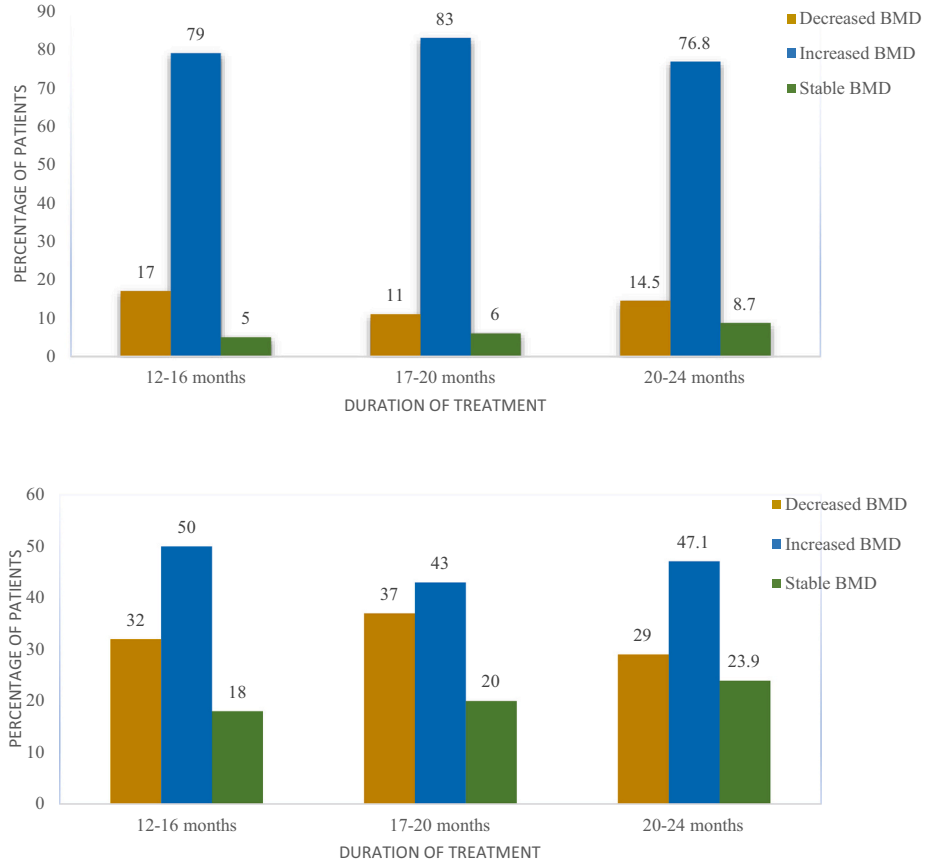


Fig. 1. Changes in T-score from baseline at the lumbar spine (A) and femoral neck (B) after 12–16 months (n = 66), 17–20 months (n = 35), and 21–24 months (n = 138) of treatment. BMD, bone mineral density, stable BMD was defined as the changes which were smaller than the least significant change of DXA machine.

phase III comparison of biosimilar and originator teriparatide products, Tabatabaei-Malazy et al. (2018) reported comparable changes in BMD at the hip, lumbar spine, and femoral neck after only six months of treatment. Here, we evaluated the impacts of biosimilar teriparatide on BMD after a longer duration of treatment, as patients received the medication for at least 12 months. Jamshidi et al. (2021) in their real-world study, demonstrated the effectiveness of the biosimilar teriparatide using two patient-reported outcomes of quality of life as measured using the EuroQol-5D (EQ-5D) health questionnaire and back pain as measured using a visual analog scale (VAS). Although patient-reported outcomes provide valuable information on the health state of the patients, BMD measurement is the most common tool for fracture risk prediction in routine clinical practice. According to a meta-regression analysis of randomized controlled trials by Black et al. (2020), significant associations exist between increases in BMD at the hip, femoral neck, and spine and reductions in vertebral and non-vertebral fractures. The authors concluded that BMD changes could be used as a surrogate endpoint to evaluate the effects of osteoporosis treatments on fracture endpoints.

The safety of the biosimilar teriparatide has been documented in an increasing number of patients both in clinical trials and in clinical use. In the phase III clinical trial comparing the biosimilar teriparatide and the originator product in 104 patients, the two treatments had similar safety profiles and were well tolerated. Recently, Jamshidi et al. (2021) monitored the safety of treatment with biosimilar teriparatide for 12 months in 193 patients with osteoporosis in a phase IV prospective cohort study and detected no new safety signals with the exposure. In a cost-utility analysis, Taheri et al. (2019) found the biosimilar teriparatide a cost-effective intervention in a cohort of women with a T-score of −2.5 or less with a prior fracture or a T-score of −3.0 or less without a prior fracture. Their results suggested that the biosimilar teriparatide reduces the risk of vertebral fractures and increases the quality-adjusted life years (QALYs), with a probability of cost-effective of 83 % at a willingness-to-pay (WTP) of three gross domestic product (GDP) per capita. In this study, we demonstrated the effectiveness of one to two years of treatment with the biosimilar teriparatide in patients with osteoporosis. These findings add to the available data for the biosimilar teriparatide and can be used in cost-benefit analyses and healthcare plans.

Our study has some limitations. The main limitation was the single-arm uncontrolled design of the study. In addition, we are not reporting fracture incidence during the study period. Moreover, in this study the percentage of increase in BMD was not assessed. The evaluation of changes in bone density before and after the use of teriparatide was based on T-score and cm^2. The amount of missing data for this evaluation was considerable and we were not able to use % increase in BMD. Finally, we could not calculate the FRAX score in more than half of the patients, as data on previous fractures or parent fractured hip was not available.

5. Conclusions

Our findings in this multi-center, single-arm study demonstrate improvements in BMD following treatment with the biosimilar teriparatide (CinnoPar®, CinnaGen Co., Iran). Our study included a reasonably large number of patients (n = 239) and further increased our understanding of the benefits of this biosimilar agent as a treatment option in patients with osteoporosis and at increased risk for fragility fractures.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Mohsen G. Soroush: Supervision. **Maryam Kheyrandish:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Soosan Soroosh:** Conceptualization, Investigation, Validation.

Declaration of competing interest

The authors declare no relevant conflicts of interest or financial relationships.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

Baumgart, D.C., Misery, L., Naeyaert, S., Taylor, P.C., 2019. Biological therapies in immune-mediated inflammatory diseases: can biosimilars reduce access inequities? Front. Pharmacol. 10, 279.

Black, D.M., Bauer, D.C., Vittinghoff, E., Lui, L.Y., Grauer, A., Marin, F., Bouxsein, M.L., 2020. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. Lancet Diabetes Endocrinol. 8 (8), 672–682.

Chen, P., Miller, P.D., Delmas, P.D., Misurski, D.A., Krege, J.H., 2006. Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J. Bone Miner. Res. 21 (11), 1785–1790.

Hernlund, E., Svedbom, A., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., Kanis, J. A., 2013. Osteoporosis in the European Union: medical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch. Osteoporos. 8, 1–115.

Jamshidi, A., Gharibdoost, F., Sedighi, S., Hajiabbasi, A., Salari, A.H., Khabbazi, A., Anjidani, N., 2021. A phase IV study of the safety and efficacy of CinnoPar® in Iranian patients with osteoporosis. J. Osteoporos. 2021, 1–6.

Leslie, W.D., Lix, L.M., Johansson, H., Oden, A., McCloskey, E., Kanis, J.A., 2011. Spine–hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos. Int. 22, 839–847.

Lim, S.Y., Bolster, M.B., 2015. Current approaches to osteoporosis treatment. Curr. Opin. Rheumatol. 27 (3), 216–224.

Malouf-Sierra, J., Tarantino, U., García-Hernández, P.A., Corradini, C., Overgaard, S., Stepan, J.J., Marin, F., 2017. Effect of teriparatide or risedronate in elderly patients with a recent pertrochanteric hip fracture: final results of a 78-week randomized clinical trial. J. Bone Miner. Res. 32 (5), 1040–1051.

Orwoll, E.S., Scheele, W.H., Paul, S., Adami, S., Syversen, U., Diez-Perez, A., Gaich, G.A., 2003. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J. Bone Miner. Res. 18 (1), 9–17.

Ostovar, A., Mousavi, A., Sajjadi-Jazi, S.M., Rajabi, M., Larijani, B., Fahimfar, N., Daroudi, R., 2022. The economic burden of osteoporosis in Iran in 2020. Osteoporos. Int. 33 (11), 2337–2346.

Panico, A., Lupoli, G.A., Marciello, F., Lupoli, R., Cacciapuoti, M., Martinelli, A., Lupoli, G., 2011. Teriparatide vs. alendronate as a treatment for osteoporosis: changes in biochemical markers of bone turnover, BMD and quality of life. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 17 (8), CR442.

Pepe, J., Colangelo, L., Biamonte, F., Sonato, C., Danese, V.C., Cecchetti, V., Cipriani, C., 2020. Diagnosis and management of hypocalcemia. Endocrine 69, 485–495.

Rachner, T.D., Khosla, S., Hofbauer, L.C., 2011. Osteoporosis: now and the future. Lancet 377 (9773), 1276–1287.

Rohrbasser, A., Harris, J., Mickan, S., Tal, K., Wong, G., 2018. Quality circles for quality improvement in primary health care: their origins, spread, effectiveness and lacunae–a scoping review. PLoS One 13 (12), e0202616.

Saag, K.G., Zanchetta, J.R., Devogelaer, J.P., Adler, R.A., Eastell, R., See, K., Warner, M. R., 2009. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six–month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 60 (11), 3346–3355.

Sheu, A., Diamond, T., 2022. Bone mineral density: testing for osteoporosis. Aust. Prescr. 39 (2).

Small, R.E., 2005. Uses and limitations of bone mineral density measurements in the management of osteoporosis. Medscape Gen. Med. 7 (2), 3.

Tabatabaei-Malazy, O., Norani, M., Heshmat, R., Qorbani, M., Vosoogh, A., Afrashteh, B., Larijani, B., 2018. Efficacy and safety of the biosimilar recombinant human parathyroid hormone Cinnopar® in postmenopausal osteoporotic women: a randomized double-blind clinical trial. Iran. J. Public Health 47 (9), 1336.

Taheri, S., Fashami, F.M., Peiravian, F., Yousefi, N., 2019. Teriparatide in the treatment of severe postmenopausal osteoporosis: a cost-utility analysis. Iran. J. Pharm. Res. 18 (2), 1073.

Tu, K.N., Lie, J.D., Wan, C.K.V., Cameron, M., Austel, A.G., Nguyen, J.K., Hyun, D., 2018. Osteoporosis: a review of treatment options. Pharm. Ther. 43 (2), 92.