Safety and effectiveness of teriparatide vs alendronate in postmenopausal osteoporosis: a prospective non randomized clinical study

Gianfilippo Caggiari¹
Paolo Tranquilli Leali¹
Giulia Raffaella Mosele¹
Leonardo Puddu¹
Francesca Badessi²
Carlo Doria¹

¹ Orthopaedic Department, University of Sassari, Sassari, Italy
² Department of Clinical Endocrinology, University of Sassari, Sassari, Italy

Address for correspondence:
Prof. Carlo Doria
Orthopaedic Department
University of Sassari
Viale San Pietro 43b
07100 Sassari, Italy
E-mail: cdoria@uniss.it

Summary

In this work we study the safety and effectiveness of teriparatide and alendronate in patients with postmenopausal osteoporosis at high risk of fracture; it was a double-blinded and it was done by examining the comparisons between teriparatide 20 μg/day and alendronate 10 mg/day. Safety and effectiveness analyses were based on data from 355 women with a mean age of 68 years. Two groups (A and B) with T-score ≤–2.5 at bone mineral density were analyzed and 3 or more vertebral fractures on radiograph. Group A: was treated with teriparatide 20 μg/day and composed from 182 women, in post-menopausal age, without a history of cancer. Group B: was treated with alendronate 10 mg/day composed from 173 women, postmenopausal age, with previous history of cancer (non-active during the study). Clinical evaluations were on bone turnover markers (alkaline phosphatase, procollagen type 1 N-terminal propeptide, and N-telopeptide cross-links), dual-energy X-ray absorptiometry and health-related quality of life (HrQoL). Safety was assessed by reporting of adverse drug reactions (ADRs). The results of this study imply that teriparatide compared with alendronate has a favorable safety profile and is effective in the treatment of patients with osteoporosis at high risk of fracture.

KEY WORDS: osteoporosis; teriparatide; alendronate; bone mineral density; vertebral fracture.

Introduction

The purpose of osteoporosis therapy is to reduce fracture risk. Osteoporosis is a serious public health concern worldwide because of the morbidity and mortality associated with fragility fracture (1, 2) which is expected to affect a large proportion of people (40-50% of women and 13-22% of men) over the age of 50 years. In 2010, osteoporosis was estimated to affect 27.6 million people in Europe. The treatment of osteoporosis consists of lifestyle measures and pharmacologic therapy. Lifestyle measures include adequate vitamin D and calcium, exercise, smoking cessation, counseling on fall prevention, and avoidance of heavy alcohol use. These measures should be adopted universally to reduce bone loss in postmenopausal women (3, 4). Once-daily administration of a parathyroid hormone fragment also increases bone mineral density in men with osteoporosis (5) and in estrogen-deficient women (6-8) and reduces the risk of fracture in postmenopausal women with osteoporosis (6). Whereas all other available treatments for osteoporosis reduce bone resorption, parathyroid hormone therapy increases bone formation. Teriparatide (recombinant 1-34 N-terminal sequence of human parathyroid hormone) is the first anabolic agent approved for the treatment of patients with osteoporosis (9) and has been reported to reduce the risk of fracture by increasing bone formation (10). It increases new bone formation by increasing osteoblast differentiation, osteoblast function, and survival. Teriparatide is recommended for patients with severe osteoporosis and can only be administered by once-daily injection in the thigh or abdomen. The recommended dose is 20 μg per day. The safety and efficacy of teriparatide has been assessed in randomized controlled trials (RCTs) and in observational studies conducted primarily in Caucasian populations. These studies have shown that teriparatide is well tolerated, reduces the risk of vertebral and non-vertebral fractures. It is known to increase bone formation and treatment of osteoporosis with PTH causes a marked increase in vertebral BMD (BMD) and levels of bone turnover biomarkers in osteoporotic patients (5-7). Alendronate belongs to the category of bisphosphonates. These have the ability to inhibit osteoclastic bone resorption. Alendronate increases bone mineral density and reduces the risk of fracture in women (3, 11) and men (9, 12) with osteoporosis. This reduces the risk of bone fractures. In our study we administered 10 mg of alendronate once daily. In the absence of specific contraindications, oral bisphosphonates are considered initial pharmacologic therapy for most postmenopausal women at high risk for fracture. We prefer oral bisphosphonates as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data.

Materials and methods

The study was conducted between January 2007 and November 2013. The cohort of 355 patients in postmenopausal age was divided into 2 groups that was selected with some inclusion and exclusion criteria, except previous history of cancer (non-acti-
ve during the study) (negative in group A and positive in group B). Inclusion criteria for this study consisted of back pain, postmenopausal osteoporosis (T-score ≤−2.5 at lumbar spine or femoral neck), the presence of 3 or more osteoporotic vertebral fractures. The exclusion criteria were: an increased risk of osteosarcoma (patients with Paget disease bone, previous skeletal exposure to radiotherapy, or previous malignant neoplasm involving the skeleton), impaired renal function, liver disease, history of diseases other than postmenopausal osteoporosis that affect bone metabolism, alcohol or drug abuse. Group A: 183 women (mean age 71±7 yrs; mean body mass index – BMI – 23.5±3.2 kg/m²), with severe postmenopausal osteoporosis (mean lumbar BMD –4.01±0.53, mean femoral BMD –3.37±0.60 and with 3 or more vertebral atrumatic fractures); Group B: 172 women matched for age (65±11.4 yrs), BMI (23.8±4.2 Kg/m²), menopausal status, affected by back pain, severe postmeno- pausal osteoporosis (lumbar spine BMD –3.98±0.46, mean femoral neck BMD –3.21±0.72 and with 3 or more vertebral atrumatic fractures). BMI, age at menopause, lifestyle habits (smoking, drinking, nutrition style, nutrition anaemia like calcium intake), family history of osteoporosis were considered. Group A were treated with 20 μg/day s.c. of recombinant human parathyroid hormone (rPHTH1–1.34), self-administered injections (group A) or 10 mg/day per os of alendronate (group B). All patient received supplemental vitamin D (600 IU per day) and supplemen- tary calcium to maintain a calcium intake of 1200 mg per day. Patients were prescribed alendronate were treated with 10 mg/day, for a maximum of 24 months. Clinical evaluations were performed before treatment and after 24 months of treatment. Safety was assessed by reporting of adverse drug reactions (ADRs), defined as adverse events for which causal relation to teriparatide could not be excluded. Effectiveness of teriparatide and alendronate treatment was as- sessed by changes in biomarkers of bone turnover, incidence of new fractures, BMD, Visual Analog Scale (VAS) score for back pain. Patients rated the severity of their back pain at baseline, at 6, 12, 18 and 24 months using this scale for pain, where a score 0 indicates no back pain and a score 100 indicates worst possible back pain. Biochemical markers of bone turnover were assessed in all patients. Alkaline phosphatase (ALP: 35–104 U/L), N-terminal propeptide of type I procollagen (PINP: 19–102 μg/l), N-terminal telopeptide cros- links (NTx: 5–65 nmol/mmol Crea) were assessed at baseli- ne, 12, 24 months (T0, T12, T24). The BMD of the lumbar spine and the proximal femur was measured by dual-energy X-ray absorptiometry at baseline and at 24 months (T0, T24). The number of new clinical fractures was counted at 6-monthly in- tervals. Incident vertebral and nonvertebral clinical fractures were defined as new fragility fractures that were reported at any postbaseline visit and were subsequently confirmed by radiographs at study sites. In accordance with the teriparatide Fracture Prevention Trial, (10) nonvertebral fractures were defined as low energy fractures, except for pathological fractures. The patients were given a questionnaire consisting of 35 questions and 5 vi- sual-analogue scale, to frame out of 5 main domains: pain, phy- sical function, social function, general health perception. All an- swers were recorded so that all items range from 1 to 5, and all answers were standardized so that 1 represents the best and 5 the worst HrQoL.

Results

This study will focus on the femoral neck and the total hip, the regions of interest considered to be the most clinically relevant (13, 14). More than half (65.4%) of the patients in group 1 have reported one or more comorbidity. The most frequently reported comorbidities were hypertension (49.6%), hepatic impairment (8.6%), and rheumatoid arthritis (4.2%). Secondary osteoporosis and glucocorticoid-induced osteoporosis were each reported in 3.0% of patients. The patients of group B had in addition to one or more morbidity (72.2%), previous history of tumors. The most frequently comorbidities in this group were hypertension (52.2%), hepatic impairment (10.9%), and rheumatoid arthritis (3.0%). Secondary osteoporosis and glucocorticoid-induced osteoporosis were each reported in 5.1% of patients. The mani- festation of adverse reactions into group A was reported in 15 (8.4%) patients. The most commonly reported ADRs in patients were hyperuricemia (1.04%), nausea (1.07%), dizziness (0.42%), headache (0.61%). Into group B, which took alen- dronate, the rate of adverse reactions was reported in 18 (10.3%) patients. In this group also the most commonly reported ADRs were hyperuricemia (2.16%), nausea (1.12%), dizziness (0.38%), headache (0.71%). There were no significant adver- sawe reactions in any patient in both groups. In this study was to evaluate percentage changes from baseline in biochemical markers of bone turnover, values of bone mineral density (mea- sured at lumbar spine and proximal femur), VAS scale, incidence of new fractures and measurements of HrQoL. There are differences between the results of bone turnover, among those obtained with the administration of alendronate and the administration of teriparatide. The levels of biomarkers for bone formation (PINP, bone ALP) were significantly increased from baseline at all time points during the study. In group A serum levels of PINP increased of 152 and 134% at T12, T24, respectively; bone ALP levels increased of 83 and 69%; NTx levels increased of 102% at T12, of 116% at T24. In group B percentage changes from baseline of serum levels of PINP were −70 and −75% at T12, T24, respectively; bone ALP levels decreased of 48 and 41%; NTx levels were reduced by 70% at T12, of 74% at T24. Mean PINP values were 41±7 μg/l at T0, 102±35 μg/l at T12, 97±27 μg/l at T24 in group A (T0 vs T12 r: 0.88, p<0.001; T0 vs T24 r: 0.86, p<0.001) and 78±16 μg/l, 22±14 μg/l, 18±10 μg/l at T0, T3, T12, T24 respectively (T0 vs T12 r: 0.76, p<0.001; T0 vs T24 r: 0.82, p<0.001). In group B mean ALP value at T0 was 68±20 U/L, 120±48 U/L at T12 and 115±38 U/L at T24 (T0 vs T12 r: 0.46, p<0.01; T0 vs T24 r: 0.85, p<0.001); instead, in group A mean ALP was 72±15 U/L at T0, 78±16 μg/l, 22±14 μg/l, 18±10 μg/l at T12 and 41±6 U/L at the end of the study (T0 vs T12 r: 0.53, p<0.001; T0 vs T24 r: 0.65, p<0.001). NTx mean values in group A were 32±6 nmol/mmol Crea, 64±14 nmol/mmol Crea, 67±25 nmol/mmol Crea at T0, T12, T24 respectively (T0 vs T12 r: 0.58, p<0.001; T0 vs T24 r: 0.50, p<0.01) while in group B NTx mean values were 54±6 nmol/mmol Crea at T0, 22±15 nmol/mmol Crea at T12 and 17±10 nmol/mmol Crea at T24 (T0 vs T12 r: 0.58, p<0.001; T0 vs T24 r: 0.70, p<0.001). The BMD values expressed in terms of T-score in our total pool displayed important changes. At month 24, lumbar spine BMD increased by 14.2% in group A compared with group B in which it increased by 7.9%. Specifically, in group A mean T-score at T0 was −3.88±0.70 and mean T-score at T24 was −3.37±0.70 (r: 0.88; p<0.001); instead, in group B, mean T-score at T0 was −3.87±0.75 and mean T-score at T24: −3.72±0.74 (r: 0.98; p<0.001). Back pain significantly (P<0.001) improved from bas- eline at all time points during the study. In the group A the mean (SD) back pain VAS score at baseline was 40.9 (27.7). The mean (95% CI) change from baseline in back pain VAS scores at 3, 12, 18, and 24 months and at the Last observation carried forward (LOCF) were −10.1 (−12.5 to −7.7), −12.4 (−15.0 to...
Discussion

The effect of teriparatide to increase bone formation, as demonstrated by studies of iliac crest biopsies, bone scans, and positron emission tomography, would be anticipated to increase bone mass and hence BMD. Areal BMD assessed by DXA at the spine and proximal femur is a standard means of identifying patients with osteoporosis, and response to therapy is often assessed by serial BMD testing (1, 15). Teriparatide was shown to have favorable safety and effectiveness profiles in osteoporotic patients at high risk of fracture. Importantly, teriparatide was well tolerated, with no new clinically significant safety concerns identified, and persistence with teriparatide treatment was similar to or higher than that reported in other studies (16, 19). Early significant increases in bone formation biomarkers were followed by subsequent increases in bone resorption biomarkers. Treatment with teriparatide resulted in a greater increase in bone mineral density (BMD). After 24 months women of group A with severe postmenopausal osteoporosis (mean lumbar BMD –4.01±0.53, mean femoral neck BMD –3.77±0.60 and with 3 or more vertebral atraumatic fractures), persistent back pain and previous treatment with bisphosphonates for osteoporosis; the women belonging group B with menopausal status, affected by back pain, severe postmenopausal osteoporosis (lumbar spine BMD –3.98±0.46, mean femoral neck BMD –3.21±0.72 and with 3 or more vertebral atraumatic fractures) previously treated for osteoporosis with bisphosphonates, we compared the results obtained from patients in group A compared to group B. From this comparison showed that teriparatide has been referred to be an efficacious treatment against new fractures, that patients with osteoporosis treated with teriparatide experience improvements in pain symptoms, making a significant change in the course of severe osteoporosis, which can lead rapidly not only to varying degrees of disability than alendronate.

Conclusion

Teriparatide increased remodelling, removed old, more fully mineralised bone matrix and improved fracture healing. Surgical fixation did not protect the others bone from probably new fracture, for this reason, are required therapies, able to enhance the bone structure at the systemic level. Therefore, this study evidences that teriparatide represents compared with alendronate, a solution that guarantees of the finest results in severe postmenopausal osteoporosis.

Author contributions

All Authors were involved in the study design, data collection, data interpretation, and statistical analysis, and contributed to the drafting of the manuscript.

Ethical considerations

This study was performed with informed consent of patients and following all the guidelines for experimental investigation with human subjects in accordance with the ethical standards of the institutional and/or national research committees and the Helsinki Declaration of 1975 and the 1983 revision of the same.

References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int. 2004;15:897-902.
2. Nazrun AS, Tzar MN, Mokhtar SA, et al. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. Ther Clin Risk Manag. 2014;10:937-948.
3. Hemlund E, Svedbom A, Ivergard M, et al. 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 Industries and Associations (EFPIA) Arch Osteoporos. 2013;8:136.
4. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int. 2005;16(Suppl 2):S3-57.
5. Krege JH, Wan X. Teriparatide and the risk of nonvertebral fractures in women with postmenopausal osteoporosis. Bone. 2012;50:161-164.
6. Kurland ES, Cosman F, McMahon DJ, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000;85:3069-3076.
7. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-1441.
8. Fahrlleiner-Pammer A, Langdahl BL, Marin F, et al. Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS) Osteoporos Int. 2011;22:2709-2719.
9. Forteo® (teriparatide [rDNA origin] injection) [prescribing information] Kobe, Japan: Eli Lilly Japan K.K.; 2014.
10. Hodsmans AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005;26:688-703.
11. Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Clin Endocrinol Metab. 2011;2011:27-2709-2719.
12. Hagiwara H. Features of limb fractures: a review of epidemiology from a Japanese perspective. J Bone Miner Metab. 2007;25:261-265.
13. Briot K, Ravaud P, Dargent-Molina P, et al. Persistence with teriparatide in postmenopausal osteoporosis: impact of a patient education and follow-up program: the French experience. Osteoporos Int. 2009;20:625-630.
14. Razbaum G, Grados F, Evans D, et al. Treatment persistence and chan-
Safety and effectiveness of teriparatide vs alendronate in postmenopausal osteoporosis: a prospective non randomized clinical study

ges in fracture risk, back pain, and quality of life amongst patients treated with teriparatide in routine clinical care in France: results from the European Forsteo Observational Study. Joint Bone Spine. 2014;81:69-75.

15. Arden NK, Earl S, Fisher DJ, et al. Persistence with teriparatide in patients with osteoporosis: the UK experience. Osteoporos Int. 2006;17:1626-1629.

16. Yu S, Burge RT, Foster SA, et al. The impact of teriparatide adherence and persistence on fracture outcomes. Osteoporos Int. 2012;23:1103-1113.

17. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38:922-928.

18. Doria C, Lisai P, Milia F, et al. Early efficacy of teriparatide in multilevel osteoporotic vertebral compression fractures treated by percutaneous vertebroplasty. Osteoporos Int. 2006;17(Suppl.2):S131.

19. Doria C, Milia F, Tidu L, et al. Clinical improvement after 18 months of therapy with teriparatide in patients affected by osteoporotic vertebral fractures: our experience in thirty women treated. Osteoporos Int. 2008;19(Suppl.2):S449.