Efficacy of teriparatide vs neridronate in adults with osteogenesis imperfecta type I: a prospective randomized international clinical study

Paolo Tranquilli Leali¹
Massimo Balsano²
Gianluca Maestretti³
Matteo Brusoni¹
Veronica Amorose¹
Emanuele Ciurlia¹
Matteo Andreozzi¹
Gianfilippo Caggiari¹
Carlo Doria¹

¹ Orthopaedic Department, University of Sassari, Sassari, Italy
² Orthopaedic Department, Santorso Hospital, Santorso (VI), Italy
³ Spinal Unit, Cantonal Hospital Fribourg, Switzerland

Address for correspondence:
Carlo Doria
Orthopaedic Department, University of Sassari, Sassari, Italy
E-mail: cdoria@uniss.it

Summary

Osteogenesis imperfecta (OI) is an hereditary disease characterized by low bone mass, increased bone fragility, short stature, and skeletal deformities, few treatment options are currently available. Neridronate is an amino-bisphosphonate, licensed in Italy for the treatment of OI and Paget’s disease of bone. A characteristic property of neridronate is that it can be administered both intravenously and intramuscularly, providing an useful system for administration in homecare. Neridronate appears to increase Bone Mineral Density (BMD) in adults with OI and reduces bone resorption by inhibition of osteoclastic activity. Teriparatide (recombinant 1-34 N terminal sequence of human parathyroid hormone) is the first anabolic agent approved for the treatment of patients with osteoporosis (7) and has been reported to reduce the risk of fracture by increasing bone formation (8). New bone formation is enhanced by a stimulation of osteoblast differentiation, osteoblast function, and survival. 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 showed that teriparatide is well tolerated and reduces the risk of vertebral and nonvertebral 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 (9-14). These data suggest a possible use of teriparatide in the treatment of this kind of disease and this study compares the classic accepted therapy using neridronate with off-label use of teriparatide.

Materials and methods

This is a multicenter, randomized, double-blind prospective study on use of teriparatide versus neridronate in the therapy of osteogenesis imperfecta type I in three European countries (Sassari-Italy; Santorso-Italy; Fribourg-Switzerland); the study protocol was approved by local ethics board as required by the individual study sites. The study was conducted in accordance with the principles of the Declaration of Helsinki (15). All patients signed informed consent at the commencement of the study before any procedures were performed. In this 24-month-
observation study we enrolled 98 patients with diagnosis of osteogenesis imperfecta type I. This study was conducted between July 1, 2013 and July 1, 2015 using a central registration method. All patients aged ≥ 25 years and had a dual-energy X-ray absorptiometry (DEXA) T-score < -2.5 (hip or spine, measured within last 2 years) and ≥ 2 fragility 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. Prevalent fractures were based on self report, skeletal radiographs or other diagnostics. This study was conducted at 3 clinical centers located in Europe. Patients were randomly assigned 1:1 to receive teriparatide 20 μg subcutaneously daily for 2 years or neridronate 100 mg infused intravenously for 30 minutes every 3 months for 2 years (Group B). All patients received supplemental vitamin D (600 IU per day) and supplemental calcium to maintain a calcium intake of 1200 mg per day. Efficacy of therapy in both groups (teriparatide group and neridronate group) was assessed by changes in bone turnover markers (BTMs), BMD, fracture incidence, Visual Analogue Scale (VAS) score for bone pain, and Short Form-8 (SF-8) health survey score for health-related quality of life (HRQoL). Serum concentration of two bone formation markers (bone-specific alkaline phosphatase [BSAP] and carboxy-terminal extension peptide of procollagen type I [PICP]) and urinary concentration of two bone resorption markers (free deoxypyridinoline [DPD] and N-terminal telopeptide [NTX]) were assessed in each group at baseline and at 6, 12, and 24 months after study initiation. Blood and urine specimens were collected in the morning at baseline. Specimens were stored at -20°C at the study site for 2 to 4 weeks and sent to a central laboratory for processing (Fribourg Laboratories, Switzerland).

In both groups of therapy patients had lumbar spine and femoral neck BMD measurements at baseline and at 24 months. BMD was assessed by DEXA using Hologic (Hologic Corp., Bedford, MA, USA), Norland (Norland Corp., Ft Atkinson, WI, USA) and GE Lunar equipment (Lunar Corp., Madison, WI, USA). The number of new clinical fractures was counted at 6-monthly intervals. Incident clinical fractures were defined as new fragility fractures that were reported at any post-baseline visit and were subsequently confirmed by radiographs at study sites. Patients rated the severity of their pain at baseline, at 6, 12, 18 and 24 months using the VAS score for bone pain, where a score 0 indicates no pain and a score 100 indicates worst possible pain. Patients rated their HRQoL at the same observation time points using the SF-8 health survey (16).

Statistical analysis

Frequency and incidence were calculated for binary variables. Mean (and standard deviation (SD) were calculated for continuous variables, except for percent changes from baseline in BTMs (where first (Q1), second (median), and third (Q3) quartiles were also calculated) and BMD (where mean and 95% confidence interval (CI) were calculated). Percent changes from baseline in BTMs and BMD were assessed using the paired t test; a P-value < 0.05 was considered statistically significant. Fracture rate was assessed using the Kaplan-Meier Method. All statistical analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC, USA).

Results

In this study, we evaluated the percentage changes from baseline in biochemical markers of bone turnover, we analyzed the values of bone mineral density (measured at lumbar spine and proximal femur), VAS scale, incidence of new fragility fractures and measurements of HRQoL.

In the teriparatide study group, level of BTMs for bone formation (BSAP and PICP) were significantly increased from baseline at all time points during the study. The median (Q1, Q3) percent change from baseline at the last observation at 24-month follow-up evaluation was 236.2% (88.7, 429.1) for BSAP and 60.9% (15.7, 97.2) for PICP (P<0.001). The levels BTMs for bone resorption (DPD and NTX) were significantly decreased from baseline at all time points during the study; the median (Q1, Q3) percent change at the last follow-up evaluation was 229.2% (131.7, 345.3) for DPD and 28.9% (4.5, 48.8) for NTX (P<0.001).

In the neridronate study group, level of BTMs for bone formation (BSAP and PICP) were increased from baseline at all time points during the study. The median (Q1, Q3) percent change from baseline at the last observation at 24-month follow-up evaluation was 178.7% (87.3, 291.4) for PICP and 37.8% (19.4, 65.2) for BSAP (P<0.05). The levels BTMs for bone resorption (DPD and NTX) were decreased from baseline at all time points during the study; the median (Q1, Q3) percent change at the last follow-up visit was 272.8% (133.9, 381.7) for DPD and 46.8% (7.9, 71.7) for NTX (P<0.05).

Mean changes in BMD at final follow-up differed significantly between two groups. BMD changes at the lumbar spine at 24 months were 5.1% with teriparatide vs -1.6% with neridronate (P<0.001).

New fragility fractures developed in fewer patients in the teriparatide group than in the neridronate group during the 24-month period, although this difference was not significant (8 [16.33%] vs 13 [26.53%], respectively) (P=0.10).

Bone pain significantly (P<0.001) improved from baseline at all time points during the study. In the group A the mean (SD) back pain VAS score at baseline was 39.8 (27.2). The mean (95% CI) change from baseline in back pain VAS scores at 6, 12, 18, and 24 months and at the last observation carried forward (LOCF) were −10.3 (−12.7 to −7.9), −12.2 (−14.8 to −9.6), −12.85 (−15.6 to −10.1), −13.5 (−16.3 to −10.7), and −13.1 (−14.8 to −11.1), respectively. In the group B the mean (95% CI) change from baseline in back pain VAS scores at 6, 12, 18 and 24 months were -10.2 (−12.1 to −8.0), -12.3 (−14.8 to 9.6), -13.1 (−16.0 to −10.8) and -13.3 (−15.1 to 11.2) respectively.

SF-8 health survey scores significantly improved following treatment with both drugs. The mean (SD) SF-8 scores at baseline in teriparatide group study ranged from 36.87 (9.11) for the physical component summary score to 45.82 (8.17) for the mental health domain. The mean (95% CI) change from baseline to the last follow-up in SF-8 scores ranged from 2.431(1.69-2.98) for the mental component summary score to 4.42 (3.68-5.10) for the role physical domain. The mean (SD) SF-8 scores at baseline in neridronate group study ranged from 37.32 (9.12) for the physical component summary score to 44.55 (8.15) for the mental health domain. The mean (95% CI) change from baseline to the last follow-up in SF-8 scores ranged from 2.47 (1.72-2.97) for the mental component summary score to 4.46 (3.64-5.07) for the role physical domain.
Efficacy of teriparatide vs neridronate in adults with osteogenesis imperfecta type I: a prospective randomized international clinical study

Discussion

Osteogenesis imperfecta is a heterogeneous disorder with a wide spectrum of clinical characters and a large genetic diversity. Although most cases of OI are caused by COL1A1/ A2 mutations, many new genetic causes have been identified in recent years. Some of these genes are related to the processing of type 1 collagen (17). An important part of managing OI and staying healthy is assembling a good health care team and having a solid working relationship with primary care doctor and medical specialists. The medical team may include an orthopedic, endocrinologist, pulmonologist, neurologist, surgeon, radiologist and nutritionist etc. Treatment is individualized and depends on the severity of the disease and the age of the patient. Treatment is directed towards preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Some people with OI undergo surgery to correct bone deformities, including scoliosis and other spinal deformities related to vertebral body fragility fractures. Actually, this kind of patients suffered by these spinal diseases may be treated by minimally invasive approach minimizing surgical trauma with fast recovery and short hospital stay (18). A common surgical procedure for OI patients, “rodding” is the placement of metal rods in the long bones of the legs. This procedure strengthens them and helps to prevent fractures. Surgical treatment is mainly performed to correct deformities and to reduce the bone brittleness as the result of bad bowing and to improve the physical condition of the individual.

The Authors of the current article have reviewed several treatments. Bisphosphonates are the widely investigated and used treatment for moderate to severe OI. Neridronate has been extensively investigated in patients with OI. In growing children, the neridronate treatment induces a rapid increase in BMD (19). A recently published study of the effects of teriparatide in adult OI has shown positive effects on BMD (20). Although bisphosphonates appear to increase BMD in adults with OI (21, 22), they reduce bone remodeling and bone formation, actions that may be problematic in the presence of underlying defects in bone formation and osteoblastic function. In contrast, in our study of teriparatide therapy, there was an anabolic pattern of change in remodeling markers that mimicked those observed in previous studies of teriparatide therapy in osteoporosis (23, 24). Moreover, the teriparatide-induced improvements in BMD in the type I OI patients were similar to those seen in osteoporosis (25) and similar to the responses recently reported in a small clinical experiment with teriparatide therapy in type I OI (26). This skeletal response to teriparatide therapy has been associated with a marked reduction in fracture risk in patients with osteoporosis. These results indicated that despite an underlying genetic defect in OI that impairs bone matrix synthesis and results in osteoblastic dysfunction and remodeling abnormalities, anabolic therapy is still able to increase bone formation and bone mass (27, 28).

Conclusion

Throughout last years, new therapeutic advantages were discovered for the treatment of osteogenesis imperfecta. Many drugs showed an increase of BMTs formation during the treatment, which are proving a mutual action over bone regeneration. At 24 months of follow-up, outcomes are moving firmly in favor of the use of teriparatide. These results are supported by statistical data and mainly, by clinical evidences and subjective health perception. SF-8 score showed that both drugs improve patient’s quality of life with better outcomes using teriparatide than neridronate. We supposed that enhancing osteoblast function and inhibiting osteoclast activity in association to an increased absorption of calcium may lead to a greater deposition of new and well mineralized bone. This feature is confirmed by significative reduction of incidence of fragility fractures in both groups with better clinical results in teriparatide group. The common features of OI and osteoporosis about bone quality and cell behavior may represent a common target for drugs therapy in association to rehabilitation programs and multidisciplinary approach.

References


Clinical Cases in Mineral and Bone Metabolism 2017; 14(2):153-156


