JCEM Case Reports, 2024, **2**, 1–4
https://doi.org/10.1210/jcemcr/luae026
Advance access publication 16 March 2024
Case Report

Teriparatide as Treatment for Severe Osteoporosis in Lung Transplant Recipients

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Abstract

Osteoporosis and osteopenia are common in lung transplant (LTx) recipients, with a significantly increased incidence compared to other non-lung solid organ transplant patients. Despite high fracture rates, including in patients treated with antiresorptive medications, there are limited data on the use of anabolic treatments in LTx recipients. We present clinical, biochemical and bone mineral density data for 3 patients with severe osteoporosis treated with teriparatide 20 micrograms daily for 18 months post-LTx. Prednisone doses ranged between 5 and 10 mg daily throughout the treatment period. All patients had previously received zoledronate (last dose 12-24 months prior to teriparatide). Bone turnover was monitored repeatedly during treatment in one patient. Following completion of teriparatide, all patients received consolidation treatment with 4 mg zoledronate. Bone density was measured prior and within 6 to 12 months after completion of teriparatide. All 3 patients experienced an increase in bone density at the lumbar spine (median +12%; range, 2%-14%) and total proximal femur (median +8%, range, 8%-10%). No adverse effects were observed. Given that severe osteoporosis is highly prevalent in LTx patients, teriparatide should be further studied as a treatment in this clinical setting. Our cases suggest it is safe and effective.

Key Words: teriparatide, osteoporosis, lung transplant, anabolic therapy

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; LTx, lung transplant; P1NP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone; TBS, trabecular bone score.

Introduction

Lung transplantation (LTx) is a life-saving treatment for end-stage pulmonary disease. In our center, and elsewhere, the number of LTx operations performed is increasing and long-term survival rates are improving. As a result, the management of long-term transplant-related complications is increasingly important. Osteoporosis is common in solid organ transplant recipients, with the highest incidence of osteoporosis and osteoporotic fracture in LTx recipients (1). Contributing factors include chronicity of the lung disease, glucocorticoid exposure, smoking, malnutrition, and exocrine pancreatic insufficiency related to cystic fibrosis (1). Standard treatment for osteoporosis in LTx recipients is with antiresorptive medications; however, despite this treatment, the incidence of fractures and associated morbidity remains high (2).

Teriparatide is a subcutaneous injection of recombinant human parathyroid hormone (PTH) that stimulates osteoblast activity, promoting an anabolic effect with increased bone formation. Teriparatide has been shown to reduce the risk of new vertebral and clinical fractures in postmenopausal women with severe osteoporosis when compared to risedronate (3). The use of teriparatide in patients with glucocorticoid-induced osteoporosis is associated with increased bone mineral density (BMD) and reduced vertebral fractures (4). However, there are limited data in the posttransplant setting, particularly LTx, where exposure to glucocorticoids is often higher than in other conditions requiring long-term immunosuppression (5, 6).

In this paper we present clinical, biochemical, and BMD data for 3 cases of severe osteoporosis in LTx recipients treated with teriparatide. Patients were supplemented with calcium carbonate 1200 mg and cholecalciferol 1000 units daily as part of routine LTx management. BMD dual-energy x-ray absorptiometry (DXA) was performed annually as part of standard LTx follow-up. Treatment for osteoporosis was decided on an individual patient basis at the discretion of the treating physician. All BMD DXA results were performed on Lunar Prodigy densitometers.

Case Presentation

Case 1

A 66-year-old female patient received a LTx for severe chronic obstructive pulmonary disease (COPD). She was diagnosed with osteoporosis prior to LTx based on screening BMD following a right foot fracture. There was a 40-pack-year smoking history, having quit 2 years prior to LTx. There was no regular steroid use prior to LTx; however, there had been intermittent short courses of prednisolone in the 2 years prior

Received: 25 January 2024. **Editorial Decision:** 6 February 2024. **Corrected and Typeset:** 16 March 2024

to LTx. Osteoporosis treatment included alendronate for 1 year prior to LTx, changed to zoledronate with first dose administered 4 months after LTx. Despite uninterrupted antiresorptive treatment, she sustained a minimal trauma radius and ulna fracture 8 months after LTx followed by further fractures of the pelvis, proximal femur, and fibula.

Case 2

A 27-year-old female patient underwent LTx on a background of cystic fibrosis. Osteoporosis was diagnosed pretransplant following multiple atraumatic rib fractures in the year prior. There was a history of steroid exposure intermittently since age 10. Previous osteoporosis treatment included 2 infusions of zoledronate, 1 in the year prior to LTx and a subsequent infusion following LTx. Five months after LTx, an additional atraumatic rib fracture occurred.

Table 1. Characteristics and bone density responses of patients who received teriparatide after lung transplant

Case	1	2	3
Age (years)	66	27	54
Sex	F	F	M
BMI (kg/m^2)	24.8	23.8	21.2
Underlying lung disease	COPD	CF	GVHD
Posttransplant time (months)	20	5	32
Prednisolone dose	5 mg	10 mg	7.5 mg
Baseline laboratory results			
Corrected calcium (RR 2.10-2.60 mmol/L, 8.42-10.42 mg/dL)	2.28 mmol/L 9.14 mg/dL	2.48 mmol/L 9.94 mg/dL	2.42 mmol/L 9.70 mg/dL
Phosphate (RR 0.70-1.50 mmol/L, 2.17-4.65 mg/dL)	1.02 mmol/L 3.16 mg/dL	1.20 mmol/L 3.72 mg/dL	0.78 mmol/L 2.41 mg/dL
25-hydroxy vitamin D (RR 50-150 nmol/L, 20-60 ng/mL)	56 nmol/L 22 ng/mL	62 nmol/L 25 ng/mL	106 nmol/L 42 ng/mL
PTH (RR 2.0-9.0 pmol/L, 18.9-84.9 pg/mL)	3.7 pmol/L 34.9 pg/mL	3.0 pmol/L 28.3 pg/mL	4.8 pmol/L 45.3 pg/mL
eGFR (RR > 60)	32 mL/min/ 1.73m^2	90 mL/min/ 1.73m^2	30 mL/min/ 1.73m^2
Lumbar spine BMD measures			
Pretreatment BMD (T-score)	1.14 g/cm^2 (−0.4 SD)	0.83 g/cm^2 (−3.0 SD)	1.38 g/cm^2 (+1.1 SD)
Posttreatment BMD (T-score)	1.28 g/cm^2 (+0.3 SD)	0.95 g/cm^2 (−2.0 SD)	1.41 g/cm^2 (+1.4 SD)
Change	+12%	+14%	+2%
Total femur BMD measures			
Pretreatment BMD (T-score)	0.62 g/cm^2 (−3.1 SD)	0.62 g/cm^2 (−3.2 SD)	0.84 g/cm^2 (−2.0 SD)
Posttreatment BMD (T-score)	0.68 g/cm^2 (−2.7 SD)	0.67 g/cm^2 (−2.8 SD)	0.91 g/cm^2 (−1.4 SD)
Change	+10%	+8%	+8%
Trabecular bone score			
Pretreatment TBS (RR >1.30)	1.35	0.90	1.40
Posttreatment TBS	1.40		1.42

Abbreviations: BMD, bone mineral density; BMI, bone mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; F, female; GVHD, graft vs host disease; M, male; RR, reference range; TBS, trabecular bone score.

Case 3

A 54-year-old male patient underwent LTx at age 52 for pulmonary graft vs host disease (GVHD) following a stem cell transplant at age 42 for acute myeloid leukemia. Prior to LTx, he had been treated with long-term glucocorticoid therapy for 10 years and diagnosed with steroid-induced osteoporosis and L2 vertebral fracture at age 46. Osteoporosis treatment prior to LTx included zoledronate, which was continued posttransplant, with the last dose administered 1 year after LTx. Despite uninterrupted treatment with zoledronate, our patient experienced a new T8 vertebral fracture.

Diagnostic Assessment

Case 1

Baseline biochemistry collected prior to teriparatide treatment (results shown in Table 1) revealed stage 3B chronic renal disease with no electrolyte abnormalities. Pre-teriparatide BMD remained low, as presented in Table 1. Baseline trabecular bone score (TBS) was 1.40 (within the normal range).

Case 2

Baseline biochemistry prior to teriparatide treatment (results shown in Table 1) revealed no abnormalities. Bone density immediately prior to teriparatide treatment remained low with T-scores < −2.5 SD. TBS was 0.90, which is low. Full bone density measurements are presented in Table 1.

Case 3

Baseline biochemistry prior to teriparatide treatment showed stage 3B chronic renal failure with normal electrolytes (Table 1). Baseline BMD measurements are included in Table 1. TBS was 1.40, which is within the normal range.

Treatment

Case 1

Given the numerous minimal trauma fractures while treated with zoledronate, osteoporosis treatment was intensified to teriparatide 20 mcg daily.

Case 2

Teriparatide 20 mcg daily was commenced 5 months after LTx in the context of the atraumatic rib fracture.

Case 3

In the setting of a new vertebral fracture, osteoporosis treatment was escalated to teriparatide 20 mcg daily.

Outcome and Follow-Up

Case 1

Teriparatide was continued for 18 months and was followed by 2 doses of zoledronate given 12 months apart. Repeat BMD assessment conducted 6 months after completion of teriparatide showed global improvements (Table 1). Calcium level remained within the reference range during the course

of treatment. Bone turnover markers were measured serially as per clinician preference, and significant increases in procollagen type I N-terminal propeptide (P1NP) and urine hydroxyproline were observed following commencement of teriparatide. Changes in bone turnover during and after treatment with teriparatide are shown in Fig. 1. Although she experienced no new fractures while on treatment with teriparatide, she subsequently sustained 2 further fractures (sub capital femur and fibula) while on zoledronate > 12 months after completion of teriparatide.

Case 2

Teriparatide was continued for 18 months and followed by zoledronate as consolidation treatment. Calcium level remained within the reference range during the course of treatment. Repeat BMD assessment 5 months after completion of teriparatide showed improvement in the lumbar spine and total hip (Table 1). No further fractures have occurred after a further 18 months of follow-up.

Case 3

Teriparatide was continued for 18 months, at which point BMD assessment was repeated and showed significant improvement in the total hip (Table 1). Calcium level remained within the reference range during the course of treatment. Consolidation treatment with zoledronate was given after 18 months of teriparatide. Longer-term follow-up is not available for this patient as he developed fatal transplant-related complications within 1 year of teriparatide completion.

Discussion

Herein, we report 3 LTx patients successfully treated with teriparatide for severe osteoporosis, exacerbated by glucocorticoid exposure. These patients represent a range of demographic characteristics, including age, sex, and underlying lung pathology. All patients achieved significant improvements in BMD at the spine and hip after 18 months of treatment. Improvements in TBS were also observed in all patients, suggesting improvements in bone quality may occur in addition to increases in bone mass. However, there is a lack of data supporting the utility of serial TBS monitoring to assess treatment effect. In all patients, treatment was well-tolerated

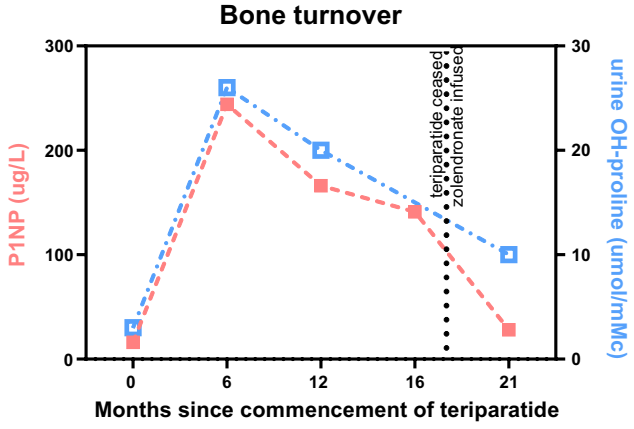

Figure 1. Serial bone turnover markers in Case 1 during treatment with teriparatide.

without clinically significant side effects and could be added to pre-existing anti-rejection and anti-infective treatment without worrisome drug interactions.

Osteoporosis is common in LTx recipients, often existing prior to transplant (2). Posttransplant care is complex, with lifelong immunosuppression and anti-infective therapies required to maintain the grafted organ. Many of these medications, particularly glucocorticoids, have potent adverse effects on bone metabolism. Supraphysiologic dosing of glucocorticoids promotes bone loss. Many LTx recipients are exposed to intermittent glucocorticoids prior to transplant and then following LTx glucocorticoids are continued lifelong, with high doses prescribed in the immediate posttransplant period to prevent rejection.

The VERO trial demonstrated the benefit of teriparatide in reducing fractures in postmenopausal osteoporosis when compared to risedronate (3). However, there are limitations of applying the results of teriparatide use in postmenopausal osteoporosis to lung transplant recipients. The benefits of teriparatide in glucocorticoid-induced osteoporosis can be extrapolated from studies in patients with rheumatological disease, although the total exposure is usually much less in these patients compared to LTx recipients (4). There are limited data on teriparatide in the posttransplant setting. A double-blind, placebo-controlled study of teriparatide in 26 deceased donor renal transplant recipients showed a trend toward reducing bone loss after transplant (5). The study duration was only 6 months, in contrast to 18 months of treatment in our cohort. After 6 months of treatment, there was a decrease in the BMD at the femoral neck in the placebo group that was not seen in the teriparatide group. BMD at the lumbar spine and distal radius/ulna remained unchanged in both groups. This may represent a protective effect against commonly occurring BMD decline at the femoral neck in the early posttransplant period (2). Paired bone biopsies from 6 patients in each group found that trabecular thickness increased more in the teriparatide group than the placebo group, but the result was not statistically significant (5). Renal transplant recipients differ from LTx recipients especially regarding the rates of hyperparathyroidism, hypercalcemia, and adynamic bone disease. The former 2 issues were accounted for in inclusion criteria for the study; however, low-turnover renal osteodystrophy was present in most of the population on biopsy, and BMD distribution showed that the samples at baseline were significantly different from a reference group of normal adult trabecular bone, with decreased calcium content and increased heterogeneity in mineralization. The lack of response to teriparatide in these renal transplant recipients may be due to ongoing PTH resistance in patients with renal osteodystrophy. Reassuringly, no adverse events were recorded in this study. Our patients had normal calcium, phosphate, and PTH values at commencement of therapy, even when renal function was reduced, making chronic kidney disease metabolic bone disease unlikely.

The only data in LTx come from a prospective longitudinal study of osteoporosis treatment in 117 consecutive patients, of whom 7 received teriparatide (6). Those treated with teriparatide had greater improvements in lumbar spine BMD compared with those treated with other drugs, but fracture incidence was similar between patients treated with teriparatide and other bone-active drugs (6).

When teriparatide was first released in the United States in 2002, there was a boxed warning for risk of osteosarcoma

based on rodent studies (7). However, since 2020, this boxed warning was removed following postmarketing surveillance studies. Organ transplant recipients are at increased risk of malignancy in the context of chronic immunosuppression. As such, the effects of teriparatide on osteosarcoma risk are unknown and may be increased relative to that in populations of postmenopausal women. To our knowledge, there have been no adverse events reported in transplant recipients related to teriparatide use and rates of malignancy.

Bone turnover makers are surrogate markers of bone formation or resorption. There are varying levels of acceptance of the clinical utility of bone turnover markers in the management and monitoring of osteoporosis treatment, with the principal clinical utility suggested to be for monitoring bisphosphonate therapy (8). In research studies, teriparatide increases bone formation, with evidence that an increase in bone formation biomarkers correlates with improved trabecular bone volume (9). Additionally, teriparatide increases makers of bone resorption to a lesser extent (10). One of our cases had serial measurements of the bone formation marker P1NP and bone resorption marker urine hydroxyproline, which demonstrated elevation with teriparatide, followed by decline with bisphosphonate use (9). Although there is limited evidence on the role of bone turnover markers in posttransplant osteoporosis, this case demonstrates a similar profile of bone turnover markers with teriparatide use as reported in postmenopausal osteoporosis research. Whether bone turnover markers are useful to guide management in individual LTx patients is unclear, and further study in this area is required.

Severe osteoporosis is highly prevalent in LTx patients, and fractures often continue to occur after treatment with antiresorptive medication. Teriparatide should be further studied as an alternative treatment in this clinical setting, as our experience in 3 patients suggests that it is safe and effective.

Learning Points

- Osteoporosis is highly prevalent following lung transplantation.
- Teriparatide was safe and effective in this case series of lung transplant recipients with severe osteoporosis.
- Anabolic agents, such as teriparatide, should be further studied in transplant recipients.

Contributors

All authors made individual contributions to authorship. L.R.: identification of the cases, review of case notes, and drafting and submission of manuscript. L.G.: identification of the cases, review of case notes, and drafting of manuscript. J.C.: involvement in cases and review of manuscript. C.M.: identification of the cases, review of case notes, drafting of manuscript, and preparation of figure.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from 2 patients; and signed informed consent could not be obtained from one patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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