Analysis of the Efficacy and Safety of Teriparatide and Alendronate in the Treatment of Osteoporosis After Renal Transplantation

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Original Paper

Introduction. Both teriparatide and alendronate were used in the treatment of osteoporosis after renal transplantation. However, there are few studies comparing their application after renal transplant surgeries. This study was carried out to compare the effect of alendronate and teriparatide on bone mineral density in the treatment of osteoporosis after renal transplantation.

Methods. This is a retrospective cohort study of 153 patients who were diagnosed with osteoporosis after receiving renal transplantation, and received either alendronate or teriparatide treatment. The demographic patient information, changes in patients' quality of life, mobility and pain scores, serum biochemical markers and bone density of lumbar spine, hip and femoral neck were measured and compared between groups a year after treatment.

Results. there were no significant differences between the two groups concerning patient demographics such as age, gender and BMI. After a year of treatment, there were no significant differences between the two groups in biochemical markers such as serum calcium, phosphorus, creatinine and 25-OH Vitamin D ($P > .05$). BMD of lumbar spine, hip and femoral neck after the treatment was significantly higher in the teriparatide group than alendronate group ($P < .05$), while the incidence of adverse effects was higher in the teriparatide group than alendronate group ($P < .05$).

Conclusion. teriparatide can be more effective than the alendronate in the treatment of osteoporosis in renal transplant patients, while having more adverse effects.

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INTRODUCTION

Solid organ transplantation is the most effective measure for treating patients with end stage organ failure, and the kidney is the most common solid organ to be transplanted throughout the world.[1,2] Due to the preexisting bone diseases and the influence of immunosuppressive agents such as corticosteroids, decrease in bone mineral density (BMD) is common in kidney transplant patients.[3-5] The most rapid bone loss occurs 6 to 12 months after operation, and BMD decreases about 10% in the first year, leading to 4 times as high risk of fracture as healthy individuals.[6] KDIGO guidelines[7] recommended a combination of bisphosphonates and vitamin D during the year following kidney transplant. Bisphosphonates can reduce the number

of osteoclasts and inhibit bone absorption. In the meanwhile, teriparatide (human parathyroid hormone 1-34) is the first drug approved by the FDA to increase osteoblast activity and promote bone formation. They are often used to prevent bone loss and treat osteoporosis in osteoporosis clinics. [8,9] However, there are few studies comparing their application after renal transplant surgeries. The current study was carried out to find a safe and more effective method to treat osteoporosis after renal transplantation.

MATERIALS AND METHODS

Patient Selection

Patients who were treated in our center with teriparatide or alendronate from January 2010 to January 2019 with osteoporosis after renal transplantation were retrospectively included in the study. The diagnosis of osteoporosis was made if T-score was lower than -2.5 at lumbar spine, hip or femoral neck, or had an incidence of fragility fracture plus T-score lower than -2. The exclusion criteria are: 1) patients who were treated with teriparatide or bisphosphonates for more than a year, or for more than a month within a year of treatment; 2) patients with serum creatinine clearance rate $\leq$ 35 mL/min, total serum calcium $\geq$ 2.75 mmol/L or < 2.0 mmol/L.

Treatment

All the procedures were approved by the ethics committee of Longyan First Hospital Affiliated to Fujian Medical University, and all the patients signed the informed consent before receiving the treatment. Patients were given all the known information regarding the current treatment effect and adverse reactions of the two drugs, and were enrolled in alendronate or teriparatide group according to the treatment retrospectively. All the patients received daily supplement of 400 IU of vitamin D and 500 mg of calcium. Patients in the alendronate group were treated with the oral application of alendronate 70 mg/week; patients in the teriparatide group received subcutaneous injection of teriparatide 20 μg/d.

Outcome Evaluation

Patient information including age, gender, body weight, height as well as time after renal transplant were recorded as basic demographics. Areal bone mineral density (BMD, g/cm^2) of L1 to L4 lumbar spine, hip and femoral neck were measured before treatment and 12 months after treatment by Hologic QDR 4500 dual-energy x-ray absorptiometry (DXA) equipment (Hologic, Waltham, Md., USA). For safety analysis, incidence of vertigo, fever, muscular pain, abdominal pain or nausea were observed and recorded during the treatment.

Changes in SF-36 life quality score,[10] visual analogue scale of pain (VAS),[11] Oswestry disability index (ODI),[12] serum biochemical markers reflecting the metabolism of bone and kidney such as parathyroid hormone (PTH), serum calcium (Sca), serum phosphorus (Sp), serum creatinine (Scr) and 25-OH Vitamin D (25OHVD) were recorded at the beginning and end of treatment. All the blood samples were taken in fasting condition, and the patients were asked to halt taking the osteoporosis medications a day before the tests.

Statistical Analysis

IBM SPSS 24.0 statistical software (IBM, Chicago, Illinoi) was used for statistical analysis, paired sample t-tests were used for within the group analysis, one way analysis of variance were used for continuous data and chi-square analysis were used for frequency counts such as gender, incidence of fracture and adverse effects. The difference was considered significant when $P < .05$.

RESULTS

General Information

A total of 153 patients were included in the final analysis. There were no significant differences between the two groups in age, gender, parathyroid hormone, SF-36, VAS and ODI, serum calcium, serum phosphorus, serum creatinine and 25-OH Vitamin D levels, BMD values in lumbar spine, hip and femoral neck before the treatment (Table 1, 2).

Immunosuppressive treatments include FK506 (Tacrolimus) (120 patients) or cyclosporin A (CsA) (33 patients), mycophenolate mofetil (MMF) (147 patients) or azathioprine (AZA) (6 patients), and Prednisone (Pred). The dosage of each agent was: CsA = 4 mg/kg/d, FK506 = 0.10 mg/kg/d, MMF = 1.0 g/d, Aza = 50 to 100 mg/d, Pred = 10-15 mg/d. There were no significant differences between the two groups concerning the immunosuppressive treatment drugs (Table 1).

Table 1. Demographic Characteristics of Included Patients

	Alendronate (n = 85)	Teriparatide (n = 68)	*P*
Age, y	48.9 ± 7.3	47.1 ± 7.1	> .05
Gender			
Male	21	17	> .05
Female	64	41	
FK506	66	54	> .05
Cyclosporin A	19	14	
MMF	82	65	> .05
Azathioprine	3	3	
SF-36	72.4 ± 10.7	73.8 ± 11.7	> .05
ODI	51.9 ± 7.2	50.6 ± 6.8	> .05
VAS	6.0 ± 1.6	5.8 ± 1.7	> .05
BMI, kg/m^2	24.5 ± 5.4	24.0 ± 4.7	> .05
MTAM, mo	62.8 ± 11.3	60.7 ± 12.2	> .05
PTH, pg/mL	26.8 ± 9.7	26.4 ± 9.3	> .05
Sca, mmol/L	2.20 ± 0.19	2.23 ± 0.15	> .05
Sp, mmol/L	1.10 ± 0.17	1.11 ± 0.20	> .05
Scr, μmol/L	91.2 ± 16.7	90.7 ± 15.6	> .05
25OHVD	52.6 ± 12.4	51.2 ± 13.6	> .05

Abbreviations: MMF, mycophenolate mofetil; SF-36, sf-36 life quality score; VAS, visual analogue pain scale; ODI, oswestry disability index; BMI, bone mass index; MTAM, mean time after transplant; PTH, parathyroid hormone; Sca, serum calcium; Sp, serum phosphorus; Scr, serum creatinine; 25OHVD, 25-OH Vitamin D

Table 2. Bone Mineral Density of Lumbar, Hip, and Femoral Neck 12 Months After the Treatment

	Alendronate	Teriparatide	*P*
Lumbar, g/cm^2			
Before	0.763 ± 0.074	0.759 ± 0.082	> .05
After	0.787 ± 0.084	0.823 ± 0.081	< .05
Hip, g/cm^2			
Before	0.735 ± 0.066	0.728 ± 0.072	> .05
After	0.762 ± 0.075	0.794 ± 0.077	< .001
Femoral neck, g/cm^2			
Before	0.735 ± 0.084	0.727 ± 0.095	> .05
After	0.763 ± 0.084	0.805 ± 0.080	< .001

Change in BMD

BMD values of lumbar spine, hip and femoral neck increased after treatment in both groups. Compared with alendronate treatment group, the BMD of lumbar spine, hip and femoral neck was significantly higher in the teriparatide group than the alendronate group (Table 2) ($P < .05$).

Other Outcome Parameters

A year after surgery, there were three vertebral and two non-vertebral fractures in the alendronate group, while there was only one Colles fracture in the teriparatide group, but the incidence of fracture was not significant between the two groups ($P > .05$, Table 3). Two patients from alendronate group and nine patients from teriparatide group reported treatment related adverse effects such as vertigo, fever and muscular pain. Five patients in the alendronate group and six patients in teriparatide group reported gastrointestinal discomfort such as abdominal pain or nausea during the treatment (Table 3). Those symptoms were alleviated after palliative treatment. Patients in the teriparatide group were more prone to developing adverse reaction ($P < .05$). 12 months after treatment, SF-36 life quality score, ODI and VAS were significantly improved compared with before the treatment ($P < .05$). In the meanwhile, SF-36, VAS and ODI were significantly better in the teriparatide group compared with alendronate group. There was significant difference in PTH level ($P < .01$), but no significant differences were found between the two groups in serum calcium, serum phosphorus, creatinine and 25-OH Vitamin D ($P > .05$, Table 3).

Table 3. Incidence of Fracture, Adverse Effects, SF-36, VAS and ODI, and the Levels of Serum Calcium, Serum Phosphorus and Creatinine After the Treatment

	Alendronate	Teriparatide	*P*
Fracture			
Vertebral	3	0	>.05
Non-vertebral	2	1	
Adverse Effects			
All	7	15	<.05
Gastrointestinal	5	6	
SF-36	87.6 ± 9.2	79.5 ± 10.3	<.001
ODI	32.6 ± 8.9	38.7 ± 9.6	<.001
VAS	3.1 ± 0.7	4.2 ± 0.8	<.001
PTH, pg/mL	25.3 ± 9.3	29.8 ± 10.7	<.001
Sca, mmol/L	2.28 ± 0.18	2.32 ± 0.20	>.05
Sp, mmol/L	1.28 ± 0.20	1.31 ± 0.26	>.05
Scr, μmol/L	82.3 ± 13.8	81.2 ± 14.3	>.05
25OHVD, nmol/L	56.4 ± 13.7	57.2 ± 14.6	>.05

Abbreviation: SF-36, sf-36 life quality score; VAS, visual analogue pain scale; ODI, oswestry disability index; PTH, parathyroid hormone; Sca, serum calcium; Sp, serum phosphorus; Scr, serum creatinine; 25OHVD, 25-OH Vitamin D.

DISCUSSION

The current retrospective study was carried out to observe the effect of bisphosphonates and teriparatide in the treatment of osteoporosis after kidney transplantation. Bisphosphonates contain two phosphonate groups that prevent loss of bone mass. There are numerous reports on the successful application of bisphosphonates after kidney

transplantation. Those studies used bisphosphonates including alendronate, pamidronate, zolendronate, rizedronate, ibandronate, which significantly reduced bone serum calcium and phosphorous levels and increased bone density. [13]

After renal transplantation, the increase of calcitriol directly affects parathyroid and inhibits the release of PTH. It also increases the absorption of gastrointestinal calcium, directly inhibiting the release of PTH and leading to significantly decreased PTH level 3-6 months after kidney transplantation.[14,15] Although the use of glucocorticoids after renal transplantation can effectively reduce the incidence of graft rejection, they also affect the survival and proliferation of osteoblasts, promote osteoblast apoptosis while enhancing the activity of osteoclasts, leading to increased bone absorption, decreased osteogenesis and reduced bone strength.[16,17] Bone loss after kidney transplantation affects the whole skeletal system, it occurs in spine at the earlier stages, leading to low back pain, loss of mobility and even fragility fractures.[18]

Currently the clinical treatment of osteoporosis is mainly focused on promoting bone formation, inhibiting bone absorption and improving the structural integrity of bone tissue.[19] Bisphosphonates can promote osteoblasts to secrete osteoprotegerin, inhibit osteoclast aggregation, affect the formation and activation of osteoclasts, and thus inhibit bone absorption. Results of the current study showed that, alendronate combined with calcium and vitamin D supplements can significantly increase bone mineral density in patients with osteoporosis after renal transplantation. This is in consistence with the previous studies.[20,21]

The main bone formation promoters are parathyroid hormone (PTH) and its analogues. PTH increases serum calcium and alkaline phosphatase levels, and stimulates osteoblast differentiation and bone mineralization through adenosine cyclophosphane system, inhibits the apoptosis of osteoblasts and promotes bone formation.[22,23] Teriparatide, the first FDA approved recombinant human PTH, is increasingly used in the treatment of osteoporosis in recent years.[24-26] Teriparatide is also recommended as a therapeutic agent in patients with low PTH after renal transplantation.[27] Cejka *et al*.[28] found no significant difference concerning bone histology, serum bone turnover markers, PTH and vitamin D levels as well as the incidence of bone fractures between patients who received PTH or placebo after renal translation. However, results on the efficacy of teriparatide in patients with osteoporosis after renal transplantation are controversial.

There are few studies comparing the efficacy and safety of bisphosphonates and teriparatide in the treatment of osteoporosis after renal transplantation. Main outcome assessment paraments of this study showed that, compared with alendronate treatment group, the improvement of BMD of lumbar vertebrae, hip and femoral neck in the alendronate group was significantly better in teriparatide group. In the meanwhile, except from PTH, other biomarkers reflecting bone metabolism and renal function did not differ between the two groups.

In the European dug administration's third stage clinical trials, teriparatide significantly reduced the fracture rate after 18 months of treatment, health related life quality scores EQ5D and EQ-VAS were significantly improved 24 months after treatment.[29] In the current study, after 12 months of treatment, SF-36 life quality score, ODI, VAS were significantly better in the teriparatide group than the alendronate group.

Side effect of the drug is one of the main impacting factors for patient compliance. In the European trial lead by Langdahl,[30] 14% of patients showed side effects of teriparatide such as headache, dizziness, nausea and vomiting. In the current study, 22% of patients who received teriparatide showed those adverse effects. There are significantly more patients with adverse reactions such as vertigo, fever, muscular pain as well as gastrointestinal discomfort in the teriparatide group than the alendronate group. However, all the adverse effects were controllable by palliative therapy.

Despite the relatively large sample size of our study, there are certain limitations to its design. The patients were not randomized, but the basic characteristics of the patients are not significantly different, providing similar baseline for two groups of patients. However, more comprehensive randomized controlled studies may be more helpful for clinical decision-making process in the future.

CONCLUSION

Results of our study indicate that teriparatide maybe more effective than alendronate in

the treatment of osteoporosis after kidney transplantation. Although there is higher chance of enduring adverse effects of teriparatide, they can be alleviated by palliative therapy.

DISCLOSURE

The authors declare that they have no conflicting of interest.

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