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ORIGINAL ARTICLE

Weekly risedronate in kidney transplant patients with osteopenia

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Summary

Daily bisphosphonate is effective in preventing and treating corticosteroid-induced osteoporosis in renal transplant recipients, although it frequently has gastrointestinal side effects. The aim was to assess efficacy and side effect profile of weekly oral risedronate. Eighty-four renal transplant patients, receiving either cyclosporin A or tacrolimus and steroids were prospectively included. The study group (39 patients) received 35 mg risedronate weekly, vitamin D and calcium, while control group (45 patients) only vitamin D and calcium. At baseline, 6 and 12 months, creatinine, calcium, phosphorus, alkaline phosphatase and iPTH were determined. Fractures and bone mineral densities were assessed by X-rays and dual-energy X-ray absorptiometry, respectively. Pain was assessed by clinical interview. Mineral bone density score increased significantly in risedronate group after 1 year. There were no differences in the incidence of fractures, although, anamnestic pain assessment revealed that 3% of treatment group reported to have bone pain compared with 18% in nontreatment group ($P < 0.05$). Follow-up calcium, phosphorus, alkaline phosphatases, and iPTH levels showed no differences from basal measures. Risedronate was well tolerated with no major side effects. Weekly oral risedronate in renal transplanted patients reduces bone mineral loss and bone pain and has an excellent side effect profile.

Introduction

Post-transplant bone disease is a major clinical problem especially in kidney transplant patients. Long-term immunosuppressive treatment with corticosteroids is a major etiological factor for osteoporosis [1]. Corticosteroids are used routinely in maintenance immunosuppressive protocols after renal transplantation (RT) and in even higher doses for the treatment of rejection episodes. Prednisone in a daily dose of 7.5 mg or greater, an amount generally exceeded in the first year after RT, is known to cause a loss of trabecular bone in most patients. Using dual-energy X-ray absorptiometry (DEXA) several studies have shown rates of bone loss of 7–10% in the first year after RT [2]. In subsequent years the rate of bone loss declines to 1–2% per year [3,4]. Renal transplant patients may be a particularly vulnerable group due to pre-existing metabolic bone disease. Several studies have demonstrated that both vitamin D and bisphosphonates can prevent or reverse accelerated bone loss after RT [5]. However, it remains unclear exactly when after RT bisphosphonates should be administered and for how long. Moreover, it is unknown if within the drug class of bisphosphonates certain drugs are more favorable than others in terms of prevention and treatment of post-transplantation bone disease.

Generally, the daily oral administration of bisphosphonates is associated with important gastrointestinal side

effects. Risedronate is a newer, more potent, orally-administered bisphosphonate with a more favorable clinical tolerance profile that can also be given on a weekly basis.

The objective of our study was to evaluate prospectively the effectiveness of the weekly administration of oral risedronate in the treatment of already established osteopenia or osteoporosis in a renal transplant population.

Patients and methods

The study project was approved by the local hospital ethical committee and informed consent was obtained from each patient. Eighty-four patients from a single center, 12–36 months after kidney transplantation, were randomized and included in this prospective study. Inclusion criteria were: age between 18 and 70 years, serum creatinine lower than 2.5 mg/dl, iPTH higher than 60 pg/ml, and a bone mineral density (BMD) showing a *t*-score of <-1. Patients with diabetes mellitus were excluded from the study. All patients were receiving immunosuppressive therapy consisting of either cyclosporin A or tacrolimus, adjusted to blood levels, and steroids (5–7.5 mg per 24 h) with or without mycophenolate mofetil. During the study period no parathyroidectomy was performed, and steroid doses were not changed.

Thirty-nine patients (19 females, 20 males) were included in the treatment group. They received 35 mg of oral risedronate weekly in combination with vitamin D and calcium (800 IU cholecalciferol and 2.500 mg of $CaCO_3$ daily). The control group (45 patients; 23 females and 22 males) received only vitamin D and calcium at the same doses.

Serum creatinine, calcium, phosphorus, alkaline phosphatase and iPTH were measured at baseline, 6 and 12 months and bone pain was assessed by clinical interview. At the same time points fractures were accessed by lumbar and femoral neck X-rays and BMD of the lumbar spine (L2-L4) and proximal femur (neck, greater trochanter, Ward's triangle and total femur) were measured by DEXA (Lunar Prodigy; Lunar Radiation Corp, Madison, WI, USA) and values were expressed as gm/cm^2 and as *z*-score and *t*-score. The primary outcome measure was the change in BMD at 6 and 12 months of follow-up.

Patients were systematically asked if they were experiencing pain during the follow-up in a double-blinded clinical interview.

Statistical analyses used for group comparisons were performed using a two-tailed Student's *t*-test for the differences between BMD measurements and chi-squared for nonparametric data.

Results

Thirty-nine patients were randomized into the treatment group. The control group consisted of 45 patients. There was no significant difference between the two groups for age, gender, weight, time after RT and laboratory values at baseline or follow-up. Baseline values are provided in Table 1. Both groups had similar degrees of pre-existing hyperparathyroidism (189 ± 89 vs.171 ± 103 pg/ml) at baseline. Follow-up calcium, phosphorus, alkaline phosphatases and iPTH levels showed no differences from basal measures. There were no deaths or allograft loss in both groups during the study period. Neither was there any significant change in renal function in either group (Fig. 1).

Bone mineral density of the lumbar spine and proximal femur showed there were no differences between the treatment and control groups at baseline. Lumbar spine

Table 1. Demographic and baseline analytical parameters of risedronate and control groups (mean ± SD). *P*-values were not statistically significant (ns) for the differences between the two groups.

	Risedronate ($n = 39$)	Control ($n = 45$)	*P*
Age (Years)	58 ± 9	55 ± 8	ns
Gender (M/F)	20/19	22/23	ns
Weight (Kg)	69 ± 13	67 ± 12	ns
Time after renal transplantation (months)	23 ± 9	21 ± 9	ns
Creatinine (mg/dl)	1.6 ± 0.7	1.7 ± 0.7	ns
Calcium (mg/dl)	9.8 ± 0.7	9.9 ± 0.8	ns
Phosphorus (mg/dl)	4 ± 0.3	4.1 ± 0.4	ns
Alkaline phosphatase (IU/l)	197 ± 64	203 ± 59	ns
iPTH (pg/ml)	189 ± 89	171 ± 103	ns
25 OH vit-D (ng/ml)	25.7 ± 8	23.6 ± 10.2	ns

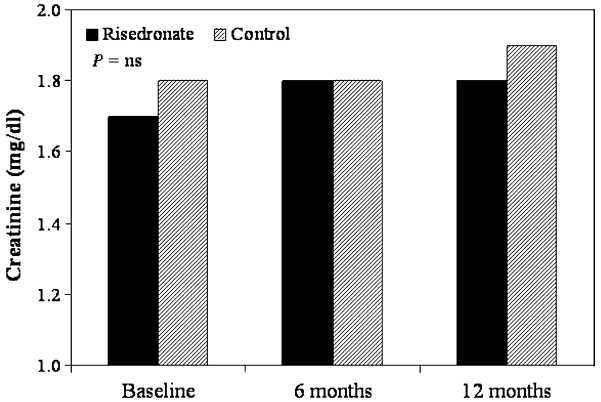

Figure 1 Creatinine values at baseline, after 6 and 12 months of follow-up did not show any significant differences between groups.

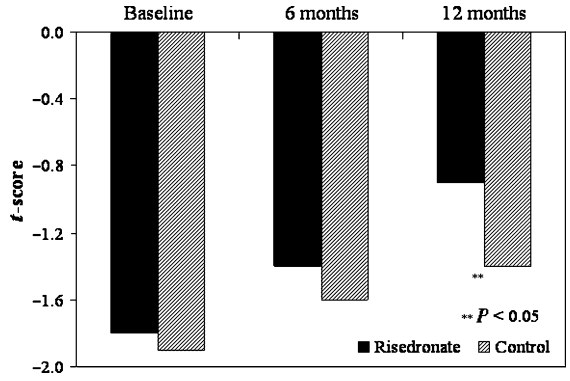

Figure 2 Bone mineral density of lumbar spine L2-L4 (medium *t*-score for each group) at baseline, 6 and 12 months of follow-up.

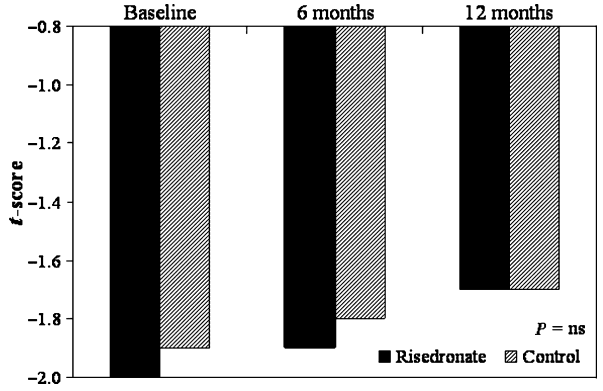

Figure 3 Bone mineral density of femoral neck (medium *t*-score for each group) at baseline, 6 and 12 months of follow-up.

t-score increased in both groups, but more so in the risedronate group, which led to a statistically significant difference ($P < 0.05$) after a 1-year follow-up (Fig. 2). Femoral neck *t*-score increased in both groups, although there were no significant differences between the two branches of the study (Fig. 3).

The incidence of vertebral fractures was lower in the risedronate group, with two vertebral fractures in the risedronate group during a 1-year follow-up, versus four vertebral fractures in the control group. This difference in the number of fractures does not reach statistical significance. No hip fractures were recorded in either group.

At baseline there was no statistical difference in the number of patients reporting to have bone pain (28% of patients in the control group versus 25% of patients in the risedronate group), however, after a 1-year follow-up, only 3% of the risedronate group patients reported to have bone pain compared to 18% in the nontreatment group, and this difference was statistically significant ($P < 0.05$). The risedronate treatment was very well tolerated with no major side effects and all patients completed the follow-up period.

Discussion

In the current study, we could demonstrate that weekly oral risedronate therapy introduced more than 1 year after kidney transplantation rapidly improves the BMD in osteopenic patients and is associated with a favorable side-effect profile. An even more relevant effect is that weekly risedronate therapy was able to significantly reduce the generalized bone pain presented by renal transplant recipients with established osteopenia or osteoporosis.

Reduction of BMD of one SD is known to increase the relative risk for vertebral and hip fractures more than twofold [6]. These findings suggest that BMD measurement is a reasonable predictor of future fracture risk.

Bone loss in renal transplant recipients is due to a combination of increased bone resorption and decreased bone formation. Factors contributing to both of these processes are evident in the early post-transplant period, especially during the first 6 months. This has been related to therapy with higher doses of steroids in this period and the effects of persistent secondary hyperparathyroidism [4]. Treatment with anti-resorptive medications such as bisphosphonates targets multiple factors that contribute to bone loss in the renal transplant population. Bisphosphonates bind to bone mineral, directly inhibiting osteoclast activity and reducing the number of osteoclasts [7]. Clinical evidence of the efficacy of bisphosphonates in the treatment and prevention of corticosteroid-induced osteoporosis has been established [8]. Treatment modalities [9], the appropriate time to begin the treatment of osteoporosis in the kidney transplant population and how to identify patients who may benefit from early prophylactic measures are still open to discussion.

In our study, we could demonstrate that weekly oral risedronate is effective in the treatment of osteoporosis when initiated 12–36 months after RT, a time by which substantial bone loss has already occurred. Although no statistically significant difference in fractures was observed, our data shows a significant improvement in BMD at the lumbar spine as well as an improvement in terms of bone pain in renal transplant patients treated with risedronate. Femoral neck *t*-score is not significantly increased in the patients under treatment compared with control because it gives more information on cortical bone, and both groups were receiving vitamin D and calcium.

Although the assessment of bone pain by clinical interview may be subjective, there was a significant difference in both groups. This finding suggests an important improvement in pain in the risedronate group and so a better quality of life.

Daily administration of bisphosphonates is limited by major gastrointestinal side effects [10,11]. However, in the present study weekly oral intake of risedronate was well tolerated without major adverse events or drop-out. This might lead to better patient compliance and subsequently to improved clinical efficacy.

In summary, our study demonstrates that the weekly administration of the bisphosphonate risedronate is a well-tolerated treatment and effective in improving BMD and bone pain in renal transplant recipients with established osteoporosis.

Authorship

JVT inclusion of candidates of the study and clinical follow-up. DF first draft of the manuscript. SP results analysis. FD validation of risedronate efficacy. JMC clinical status of patients included in the study. SR evaluation of mineral bone density. Federico Oppenheimer coordination of the study.

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