Pamidronate used to attenuate post-renal transplant bone loss is not associated with renal dysfunction

Sally Lee, Daniel Glicklich and Maria Coco

Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, USA

Abstract
Background. Pamidronate is a second-generation bisphosphonate that has been used to attenuate post-renal transplant bone loss, but its effect on the function of the renal allograft is unclear. Therefore, we evaluated the long-term renal function in 57 subjects who had participated in a prospective, randomized clinical trial using pamidronate to attenuate bone loss in the renal transplant recipient.

Methods. Thirty subjects (PAM) received intravenous pamidronate, 60 mg at baseline post-transplant and 30 mg in months 1, 2, 3 and 6 post-transplant, while 27 subjects (CON) did not receive pamidronate. We followed renal function, need for renal replacement therapy following transplant rejection, and mortality for 3 years following the start of the original study.

Results. PAM did not have increased incidence of renal dysfunction or mortality compared with CON at any time point during the 3 years of follow-up. The incidence of proteinuria was also not different between the two groups.

Conclusions. The prophylactic use of pamidronate in the above doses to attenuate bone loss in renal transplant recipients is not associated with higher incidence of renal dysfunction or mortality in a 3 year follow-up study. These findings may support the use of bisphosphonates in the treatment of early renal transplant-related bone loss.

Keywords: bisphosphonates; renal osteodystrophy; renal transplant

Introduction
Bisphosphonates bind to the surface of bone undergoing resorption and impair the ability of the osteoclast to form ruffled borders while inhibiting production of protons necessary for bone resorption [1]. They are useful in treating conditions that promote excessive bone resorption and hypercalcemia, such as Paget’s disease, osteoporosis and various malignancies. However, high dose bisphosphonates have been implicated as a cause of collapsing focal segmental glomerulosclerosis and toxic acute tubular necrosis in patients treated for hypercalcemia of malignancy [3].

Recipients of successful renal transplants experience rapid bone loss during the first 12–18 months [4], and may continue to experience persistent bone loss for many years [5,6]. This bone loss may be attenuated by bisphosphonates [7–10]. Bisphosphonates have been reported to ameliorate bone loss in renal transplant recipients with largely favourable results [7,8,10], although they may be associated with oversuppression of bone activity and adynamic bone disease [8].

We have shown that pamidronate lessens short-term bone loss in renal transplant recipients, when given in low dosage [8]. However, its long-term effect on renal function in the renal transplant population is unclear. We report the 3 year outcome on renal function of our original cohort who had participated in the randomized, controlled study of pamidronate given in the first 6 months following renal transplant [8].

Subjects and methods
Fifty-seven subjects completed a prospective, randomized, controlled trial that evaluated the effect of pamidronate on bone mineral density and bone histology. The study was approved by the Montefiore Institutional Review Board. Inclusion criteria encompassed all adult renal transplant recipients who were haemodynamically stable perioperatively. Exclusion criteria included inability to return for regular follow-up during the study period. The subjects were recruited between August 1, 1999 and November 30, 2000, and followed for 3 years from entry into the study.

The subjects had been randomized to one of two groups. Thirty subjects (PAM) received intravenous pamidronate 60 mg within 48 h after transplantation followed by 30 mg
at months 1, 2, 3 and 6 for a total of 180 mg. The dose was the same in all the subjects. Twenty-seven controls (CON) did not receive pamidronate [8]. These subjects were followed for routine care at the renal transplant clinic at Montefiore Medical Center for the next 3 years.

Routine blood chemistries and urinalyses were obtained at least every 6 months. Creatinine clearance was estimated using the Cockgroft–Gault formula, corrected for gender at each time point evaluated. Proteinuria was assessed on routine urinalysis and scored semiquantitatively (0; 30 mg/dl; 100 mg/dl; and 300 mg/dl). The subjects were monitored for the eventual need for renal replacement therapy. Episodes of renal dysfunction were followed with renal allograft biopsies and treated as indicated for diagnosed acute rejection.

Charts were reviewed for adverse outcome such as death or graft loss. Morbidity and mortality outcomes were confirmed by telephone interviews with a family member if the event took place outside the Montefiore Medical Center.

Statistical analyses

Differences between the PAM and CON groups at 6 months and yearly time points were compared by independent \( t \)-test. The effect of pamidronate use on renal function at 36 months was analysed with univariate linear regression. Multivariate linear regression analysis was used to determine if serum creatinine and creatinine clearance at year 3 was influenced by independent variables of pamidronate use, rejection episodes and proteinuria. The statistical program SPSS-8 was used to analyse the data. Means are reported as ± SD.

Results

Fifty-seven subjects had functioning grafts at the beginning of the first year. 56 subjects were present in the second year and 49 subjects were available at the third year. Twenty-six subjects from PAM and 23 from CON remained.

In PAM, four subjects had lost their allograft by the end of the third year due to non-compliance and chronic rejection. One subject with a functioning renal graft expired from congestive heart failure at the 36th month. In CON, one subject lost his graft at 9 months and one lost her graft before the end of the second year. Both subjects subsequently died from sepsis before the end of the second year. Two more subjects lost their grafts before the end of the third year due to chronic rejection and non-compliance with immunosuppressive therapy. There was no significant difference between the two groups in mortality or graft loss.

After the first year of the study, four subjects in PAM and two subjects in CON were given oral bisphosphonates by their private nephrologists in the community.

There was no difference in serum creatinine or creatinine clearance at any time point between the two groups during the period of observation (Table 1). Similarly, there was no difference in the incidence of proteinuria (Figure 1) or rejection rate between the two groups at any time point. Transplant biopsies, done in the setting of acute renal dysfunction, confirmed acute rejection. Serum chemistries remained similar.

Univariate regression analysis with creatinine at 36 months as the dependent variable and pamidronate use as the independent variable was not significant.
Multivariate regression analyses showed creatinine at year 3 was dependent on urinary protein and episodes of rejection only (Table 2). Similarly, creatinine clearance at 36 months was dependent on urinary protein and episodes of rejection only (Table 2).

**Discussion**

In contrast to reports of renal toxicity associated with the use of intravenous bisphosphonate therapy for hypercalcaemia in patients with underlying malignancies, our study shows that short-term use of low dose pamidronate, total 180 mg, was not associated with increased incidence of renal dysfunction or mortality in 30 renal transplant recipients who had received a short-term course of intravenous pamidronate as compared with the 27 untreated control subjects. We found no difference between the control and treated group with respect to rejection, graft loss, serum creatinine and proteinuria at any time point in the 3 year follow-up. Fan et al. also report no difference in creatinine at 4 years follow-up in their smaller group of 17 males (nine pamidronate and eight controls) after receiving one dose of pamidronate (0.5 mg/kg) before the renal transplant and an additional dose 1 month postoperatively [11]. Our larger experience, with 49 male and female subjects, confirms these observations and in addition reports no difference in proteinuria between the group treated with pamidronate and the control group.

Proteinuria is a marker of renal damage, monitored by transplant nephrologists to detect chronic allograft nephropathy or recurrence of renal disease [12]. Massive proteinuria was reported in a case series of seven patients (six with multiple myeloma and one with metastatic breast cancer) who had been given pamidronate in total doses ranging from 1350 to 6660 mg over a period of 11–49 months prior to renal biopsy. Kidney biopsy showed collapsing focal segmental glomerulosclerosis [2]. Proteinuria was also reported in patients who were given zolendronate, a third-generation bisphosphonate, and who subsequently developed renal dysfunction and acute tubular necrosis [3]. These seven patients (six with multiple myeloma and one with metastatic breast cancer) had been treated with pamidronate at a total dose ranging from 180 to 4140 mg over 2–46 months before being switched to zolendronate 16–32 mg total dose over the next 2–8 months. Of note, these patients had underlying malignancies and had been treated with nephrotoxic agents such as chemotherapy and non-steroidal anti-inflammatory agents, which could have contributed to or predisposed the patients to the nephropathy. The fact that our subjects did not demonstrate any adverse nephrotoxic effect may be because they did not have a predisposing malignancy or use medications that could have compromised renal function. The adverse nephrotoxic effect of pamidronate may also have been dose related since the reported cases of collapsing focal segmental glomerulosclerosis were seen with high dose pamidronate used for prolonged periods of time [2]. Doses used for treatment of hypercalcaemia due to malignancy are much higher and given for a more prolonged period of time than those used for treatment of transplantation-associated bone loss [7,8].

In conclusion, our follow-up study of renal transplant recipients treated with a short course of pamidronate for 6 months following renal transplantation does not demonstrate any increased incidence of long-term renal dysfunction when compared with the control group who did not receive this bisphosphonate. Cautious use of low dose and short-term bisphosphonates may be useful after renal transplantation to preserve bone mass without endangering renal function.

Conflict of interest statement. None declared.

**References**


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