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Bisphosphonates as a Tacrolimus-Sparing Strategy in Kidney Transplantation

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Objectives : The chronic toxicity of tacrolimus makes its sparing a crucial consideration for kidney transplant recipients (KTRs). Previous research has indicated a positive association between bisphosphonate use and favorable graft outcomes in KTRs. Therefore, our study aimed to investigate whether bisphosphonate use impacts the relationship between tacrolimus trough levels (TTLs) and graft outcomes in KTRs.
Methods : We conducted a retrospective study encompassing 1,657 KTRs who were administered tacrolimus-based immunosuppressive therapy. The primary exposure was characterized by a time-dependent cross-product of TTLs (low TTLs vs. normal-high TTLs with a reference of 6ng/mL) and the use of bisphosphonate. The study had two primary outcomes: (1) overall graft loss, defined as either the occurrence of patient death or conversion to kidney replacement therapy, and (2) reaching an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m².
Results : Over a cumulative total of 11,211.8 person-years, overall graft loss were observed in 183 patients, equating to 11.0% of the cohort. In multivariable Cox regression analysis, it was noted that normal to high TTLs, in the absence of bisphosphonate use, were associated with a reduced risk of overall graft loss (Hazard Ratio [HR], 0.61; 95% Confidence Interval [CI], 0.43-0.87) compared to low TTLs without bisphosphonate use. The use of bisphosphonate in conjunction with normal to high TTLs correlated with an even further diminished risk of overall graft loss (HR, 0.36; 95% CI, 0.16-0.83) in comparison to low TTLs without bisphosphonate use. In low TTLs, the administration of bisphosphonates was associated with a reduced risk of overall graft loss than bisphosphonate non-use. Similarly, this trend was observed in analysis for the occurrence of eGFR of less than 30 mL/min/1.73 m^2.
Conclusions : The use of bisphosphonate was associated with favorable graft outcomes, even with a low TTLs. Incorporating bisphosphonate to a conventional immunosuppressant regimen could potentially reduce tacrolimus requirement.

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Table. Cox regression analysis for kidney outcomes according to mean tacrolimus trough levels and bisphosphonate use

	Overall graft loss				eGFR <30 mL/min/1.73 m²			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
TTL <6 without BPP	Reference		Reference		Reference		Reference	
TTL ≥6 without BPP	0.70 (0.49 - 0.99)	.045	0.61 (0.43 - 0.87)	.006	1.05 (0.82 - 1.35)	.675	0.98 (0.76 - 1.25)	.848
TTL <6 with BPP	0.23 (0.13 - 0.43)	<.001	0.26 (0.14 - 0.49)	<.001	0.27 (0.17 - 0.45)	<.001	0.34 (0.21 - 0.56)	<.001
TTL ≥6 with BPP	0.38 (0.17 - 0.86)	.020	0.36 (0.16 - 0.83)	.016	0.30 (0.14 - 0.64)	.002	0.33 (0.15 - 0.71)	.004

Note: Adjusted for recipient age, recipient sex, donor age, donor sex, recipient-donor relation (deceased, living-related, or living-unrelated), HLA mismatch (0, 1-3, or 4-6), ABO mismatch (identical, compatible, incompatible), DM history (none, pre-transplantation, or post-transplantation), baseline eGFR, and transplantation year.
Abbreviations: BPP, bisphosphonate; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; HR, hazard ratio; TTL, tacrolimus trough level.