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臨床組-從業

探討腎臟移植病人Tacrolimus濃度劑量比與移植器官功能表現之關聯性

Association Between Tacrolimus Concentration-to-Dose Ratios and Graft Function Among Kidney Transplant Recipients

張鏞璘[1*]、王華斌[2,3]、項怡平[1]、吳幸綿[4]、張立青[5]

[1]義大醫院藥劑部、[2]義大醫院泌尿科、[3]義大醫院器官移植中心、[4]義大醫院醫檢部、[5]義守大學醫學院

Background

Tacrolimus is the keystone immunosuppressive drug administered after solid organ transplantation. Due to narrow therapeutic range of tacrolimus, dosage adjustment should be based on the result from therapeutic drug monitoring. Concentration-to-dose ratios (CDR) of tacrolimus is considered as one of surrogate indicators due to limited access to metabolic enzyme CYP3A5 gene polymorphism examination [1,2]. However, there is lack of relevant data mentioned about the utility of CDR in Taiwan. The aim of current study is to explore the relation between tacrolimus CDR and graft and patient outcomes in kidney transplant recipients (KTRs).

Method

This is a mono-center, non-intervention, retrospective cohort study. Inclusion criteria was consisted of adult KTRs with triple maintenance therapy of tacrolimus, mycophenolate, and prednisolone. Tacrolimus CDR was calculated from dosage and trough concentration measured between 1 and 12 months post-transplantation. Patients were divided into two groups according to their mean CDR value: high-CDR and low-CDR groups. The primary outcomes are incidence of biopsy-proven acute rejection (BPAR) at 1 year posttransplant and change in graft function, defined as difference eGFR between 1 and 12 months post-transplantation.

The secondary outcomes include BPAR, infection rates and concomitant diseases within 3 years posttransplant. Statistical analysis was using independent sample t test, Pearson chi-square tests or Fisher's exact test and Logistic regression, respectively. All analyses were performed using IBM SPSS 18.

Results

A total of 90 patients were included in the analysis. High-CDR group consisted of 50 patients with CDR above 1.29 ng/mL/mg. The mean CDR value in high-CDR group was 2.29±0.94 ng/mL/mg compared with 0.92±0.19 ng/mL/mg in low-CDR group (p<0.0001). The mean trough concentration of tacrolimus in high-CDR and low-CDR groups were respectively 7.83±3.13 ng/mL and 6.79±2.60 ng/mL (p<0.0001). Targeted trough level has been achieved in both groups. The BPAR at 1 year posttransplant was 6.0% in the high-CDR group and 15.0% in the low-CDR group (p=0.179). The same pattern of BPAR has been observed at three years post-transplant (20.0% vs. 10.0%, p=0.180). The incidence of graft function improvement was significantly higher in high CDR patients than in low CDR patients (OR 2.96, 95% CI 1.05-8.35, p=0.040).

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Clinical interested outcomes including 1 year post-transplant infection rates of cytomegalovirus (12.0% vs. 5.0%, p=0.692) and BK polyomavirus (4.0% vs. 0.0%, p=0.517) both were higher in high-CDR group but statistically non-significant. The incidence of common complications after long-term tacrolimus therapy were similar in both groups.

Table 1. Baseline characteristics of low-CDR group and high-CDR group

	Low-CDR (n=40)	High-CDR (n=50)	*p* value
Tacrolimus related			
Mean trough ± SD, ng/ml	6.79±2.60	7.83±3.13	<0.0001
Mean CDR ± SD, ng/ml/mg	0.92±0.19	2.29±0.94	<0.0001
Recipient related			
Male sex, N (%)	22 (55.0%)	30 (60.0%)	0.633
Mean age ± SD, yrs	49.28±10.22	51.02±9.40	0.402
Mean BW ± SD, kg	60.68±13.49	66.74±10.83	0.020
Transplant related			
Deceased donor, N (%)	37 (92.5%)	41 (82.0%)	0.145
eGFR change ± SD, ml/min/1.73m^2	4.21±12.27	8.10±11.42	0.124

Table 2. Primary end points and safety outcomes

	Low-CDR (n=40)	High-CDR (n=50)	*p* value
Primary end points			
Increased eGFR, N (%)	27 (67.5%)	43 (86.0%)	0.036*
BPAR, N (%)	6 (15.0%)	3 (6.0%)	0.179
Infection			
CMV viremia, N (%)			
1 year post-transplant	2 (5.0%)	6 (12.0%)	0.692
3 year post-transplant	7 (17.5%)	7 (14.0%)	0.308
BK polyomavirus, N (%)			
1 year post-transplant	0 (0.0%)	2 (4.0%)	0.517
3 year post-transplant	2 (5.0%)	6 (12.0%)	0.458
Concomitant disease			
Hypertension, pre-Tx	21 (52.5%)	30 (60.0%)	0.476
1 year post-transplant	24 (60.0%)	30 (60.0%)	1.000
3 year post-transplant	24 (60.0%)	29 (58.0%)	0.848
Diabetes, pre-Tx	3 (7.5%)	5 (10.0%)	0.728
1 year post-transplant	5 (12.5%)	8 (16.0%)	0.639
3 year post-transplant	7 (17.5%)	13 (26.0%)	0.335
Dyslipidemia, pre-Tx	6 (15.0%)	10 (20.0%)	0.538
1 year post-transplant	16 (40.0%)	11 (22.0%)	0.064
3 year post-transplant	18 (45.0%)	23 (46.0%)	0.925
Hyperuricemia, pre-Tx	1 (2.5%)	8 (16.0%)	0.040
1 year post-transplant	5 (12.5%)	5 (10.0%)	0.746
3 year post-transplant	10 (25.0%)	11 (22.0%)	0.738

Conclusion

High tacrolimus CDR (>1.29 ng/mL/mg) was strongly associated with better graft function and trend of BPAR reduction. Tacrolimus CDR may be an easy and potential monitoring tool to help identify high-risk KTRs in the first year post-transplant.

References:

[1] Pharmacotherapy. 2019;39(8):827-36.

[2] Expert Opin Drug Saf. 2019;18(4):285-94.