INFLUENCE OF CYTOCHROME P450 3A5 (CYP3A5) GENETIC POLYMORPHISM ON SHORT-TERM OUTCOMES IN KIDNEY TRANSPLANT RECIPIENTS TREATED WITH TACROLIMUS

T. Linares, N. Macías, E. Torres, L. Sánchez-Cámara, A. García-Prieto, E. Hurtado, M. Martín, M. Rodriguez, F. Anaya.
Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

INTRODUCTION

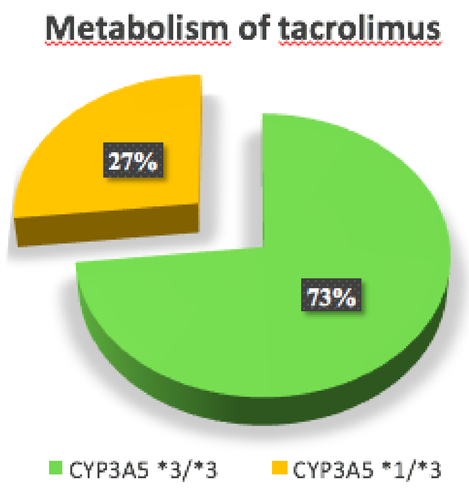
Tacrolimus is a key component of immunosuppression regimes in kidney transplantation to prevent graft rejection. It has been observed that tacrolimus dose necessary to achieve target blood levels is highly variable. One of the major factors affecting the bioavailability of tacrolimus is a polymorphism in CYP3A5 gene, which allows to classify patients in poor, intermediate and extensive metabolizers. The aim of the study was to compare the evolution of kidney transplant patients according to tacrolimus metabolism.

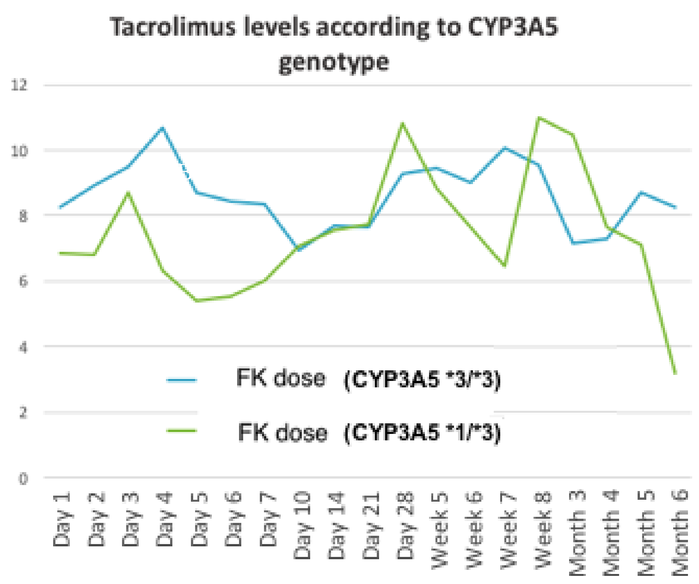
METHODS

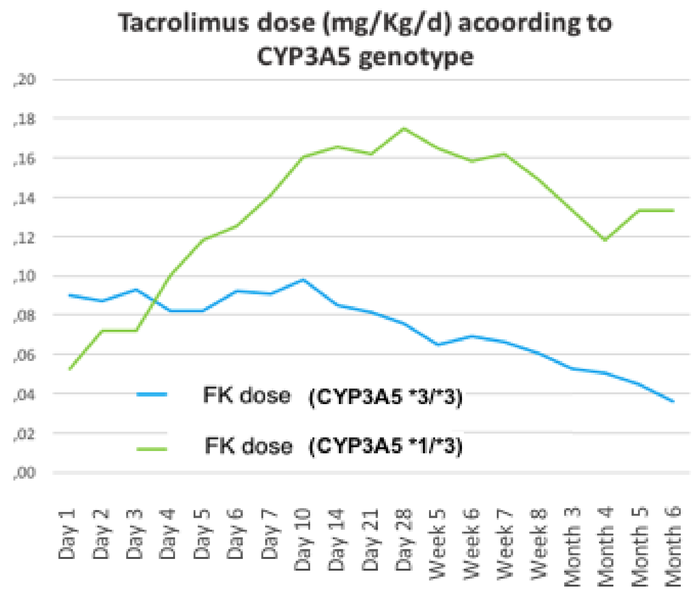
A single-center, retrospective observational study was performed in thirty deceased donor kidney transplant recipients.
Donors and recipients characteristics at the time of transplantation, periodic determinations of renal function (eGFR), level of proteinuria, tacrolimus dose and blood levels (daily during the first week, weekly in the first two months and monthly until the sixth month), post-transplant complications and changes of immunosuppression regimen were collected. Short-term evolution was compared depending on CYP3A5 gene polymorphisms. Follow-up period was 5 (4 – 6) months.

RESULTS

73.3% of patients were poor metabolizers and 26.7% were intermediate metabolizers. The prevalence of patients with intermediate clearance was higher in african-american patients (75% VS 23.8%, p 0.019) compared to other races. Intermediate metabolizers required higher dose of tacrolimus to achieve trough blood levels since the fifth day (day 5: 4.9±1.7 VS 2.9±0.6 mg/d, p 0.037; day 7: 10.7±4.4 VS 6.4±2.5 mg, p 0.003; day14:12.7±2.9 VS 6.5±2.5 mg, p<0.001; day 28:13.7±2 VS 5.7±2.1 mg, p<0.001), differences that were maintained until the end of the follow-up (p<0.001). New-onset post-transplantation diabetes mellitus was more common among intermediate metabolizers, but did not reach statistical significance (60% VS 25%, p 0.065).
There were no differences in sex, chronic kidney disease etiology, cardiovascular risk factors, previous kidney transplants, type of donation, HLA mismatches, CMV serostatus, induction immunosuppression with polyclonal, delayed graft function, use of mTOR-inhibitors, urological complications, incidence of acute rejection or calcineurin inhibitor toxicity.







Basal characteristics	CYP3A5 *3/*3 N=22	CYP3A5 *1/*3 N=8	p (Sig.)
Age (years)	50,9 ± 16,8	54,5 ± 15,1	ns
Men	16 (72,7%)	8 (100%)	ns
BMI (kg/m^2)	27,2 ± 5,6	26,2 ± 3,3	ns
African-american race	1 (4,5%)	3 (37.5%)	0.019
High blood pressure	21 (95,4%)	8 (100%)	ns
Post-transplant diabetes mellitus	3 (13,6%)	2 (25%)	ns
Residual diuresis (ml/day)	388 ± 470	950 ± 752	0.024
Donor creatinine (mg/dl)	0,76 ± 0,25	1,08± 0,67	ns
Glomerular sclerosis (%)	6,5 ± 9,6	7,3 ± 8,8	ns
Asystolic donor	5 (22,7%)	3 (37,5%)	ns
Expanded criteria donors (%)	17 (77,3%)	7 (87,5%)	ns
Age difference between donor and recipient (years)	13,7 ± 9,4	11,5 ± 7,2	ns
HLA mismatch (n)	4,1 ± 1,4	4 ± 1,7	ns
Polyclonal antibodies induction	8 (36,4%)	4 (50%)	ns
Initial dose of FK (mg(Kg))	0,104 ± 0,041	0,059 ± 0,047	0.018
Retarded FK introduction	3 (13,6%)	3 (37,5%)	ns

Post transplant complications	CYP3A5 *3/*3 N=22	CYP3A5 *1/*3 N=8	p (Sig.)
POST TRANSPLANT INFECTIONS	15 (68,18%)	4 (50%)	ns
Number of post transplant infections (n)	1,68 ± 1,7	1,37 ± 1,8	ns
ACUTE HUMORAL REJECTION	7 (31,8%)	1 (12,5%)	ns
UROLOGICAL COMPLICATIONS	6 (27,8%)	2 (25%)	ns
POST TRANSPLANT DIABETES MELLITUS	2 (9%)	3 (37,5%)	0.065

CONCLUSIONS

We conclude that CYP3A5 gene polymorphisms influence in the tacrolimus dose requirements to achieve therapeutic blood levels. Differences in tacrolimus clearances according to these polymorphisms appear to be more since the first week after transplantation. Appropriate monitoring and follow-up may guarantee similar plasmatic levels and graft function despite these differences. Knowing the CYP3A5 genotype prior to transplantation could modify management of post-transplant, and may lead to lower the incidence of nephrotoxicity and reduce acute rejection rates. These aspects as well as its economic impact, requires to be evaluated in further studies.

1. Birdwell KA et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. Clin Pharmacol Ther 2015;98(1):19-24.
2. Khemjira Yaowakulpatan et al. Impact of CYP3A5 polymorphism on trough concentrations and outcomes of tacrolimus minimization during the early period after kidney transplantation. Eur J Clin Pharmacol (2016) 72:277–283 .
3. H. Kato et al. Long-Term Influence of CYP3A5 Gene Polymorphism on Pharmacokinetics of Tacrolimus and Patient Outcome After Living Donor Liver Transplantation. Transplantation Proceedings (2016), 48, 1087-1094.
4. N. Pallet et al. Long-Term Clinical Impact of Adaptation of Initial Tacrolimus Dosing to CYP3A5 Genotype. American Journal of Transplantation 2016; XX: 1–6.

54 ERA
813--SP
Renal transplantation - Treatment & immunosuppre
TANIA LINARES
DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.