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Effects of *CYP3A5* and *ABCB1* Genetics Variant on Tacrolimus Pharmacokinetics in Algerian adult Kidney Transplant Patients

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Abstract

Objective*: The aim of this study is to determine the impact of CYP3A5 c. 6986A>G and ABCB1 c. 3435C>T polymorphisms on Tacrolimus (Tac) pharmacokinetics in Algerian kidney recipients transplant. Pharmacogenetics methods may be used prospectively to aid dose selection and individualize immunosuppressive therapy.*

Methods: *Sixty three kidney transplant patients from West Algerian population were enrolled in the study. The Tac pharmacokinetic parameters were calculated from patients blood. The Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique and data were analyzed by χ2.*

Results: *Our findings suggest that there is a significant distribution of TAC Concentration/Dose Ratio in Days 30 to 90 for these polymorphisms. However, at the sixth month after transplantation the Tac concentration/Dose Ratio present a significant distribution for only the CYP3A5 c. 6986A>G polymorphism.*

Conclusion: *We have shown, for the first time in Algerian population that theses polymorphisms are not an important genetic factor on Tac pharmacokinetics.*

Keys Words: *Kidney transplant, CYP3A5, ABCB1, Tacrolimus, cyclosporine, Algeria, polymorphism.*

Introduction

The Tacrolimus (Tac) is an effective immunosuppressive drug which is widely used in kidney transplant recipient [(1)]. This drug binds to another immunophilin, the FK506-binding protein 12 (FKBP12), to form a complex which inhibits the calcineurin pathway [(2)]. Tac blood concentrations has a great importance to avoid rejection and dose-related adverse effects after transplantation [(3)]. Underexposure of this molecule can cause failure of immunosuppressant and acute rejection in patients. However, its overexposure may put patients at risk for toxicity. Various factors, such as age, sex, drug interactions may lead to an effective dosage of Tac variability [(4)].In addition to these factors, other genetic factors can play a critical role. To date, the most studied genes are: the cytochrome CYP 3A5 and the adenosine triphosphate-binding cassette B1 gene (*ABCB1*) genes, that encoded two proteins implicated in Tac metabolism.

Many researchers studied the role of the rs776746 polymorphism of CYP3A5 gene (*CYP3A5* c. 6986A>G) on tacrolimus response outcome. This polymorphism in intron 3 leads to a non functional protein (allele*3). The patients that show the allelic variant CYP3A5*3 in the homozygous state (G/G) are slow metabolizers of Tac, and present an increase of Tac concentration in blood. In opposite, heterozygotes A/G (or CYP3A5*1/CYP3A5*3 alleles) are intermediate metabolizers, while those homozygosis A/A (or CYP3A5*1/CYP3A5*1 alleles) are normal metabolizers [(5)].

The *ABCB1* gene or multidrug resistance-1 (*MDR-1*) gene, encodes the P-glycoprotein (P-gp) which represent an efflux pump in many organs and tissues. The most commonly studied *ABCB1* polymorphisms include a C to T substitution at position 3435 on exon 26 (rs1045642), leading to a synonymous amino acid in P-gp. The variant 3435 C> T affect the expression of the messenger RNA by influencing its stability [(6)] and the specificity of P-gp with its substrates [(7)].

The aim of the current study is to determine the impact of *CYP3A5* c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms on tacrcolimus pharmacokinetics.

2. Materials And Methods

2.1. Study design

This study was developed as a retrospective study including 62 kidney transplanted patients from West Algeria and was conducted between January 2011 and February 2014 at pharmacology service of Hospital-University Establishment of Oran (EHU Oran, Algeria). Each patient gave informed consent to participate in the study.

These patients were treated with tacrolimus-based immunosuppressive regimens by twice daily oral administration. For all patients, the initial dosage of tacrolimus was 0.1 mg/kg/d and the dosage was adjusted according to target trough blood concentration of 8 to 12 ng/ml during the first six months, and 3 to 7ng/ml more than one year. Tacrolimus trough concentration was measured using the Emit® 2000 tacrolimus specific assay (Viva-E analyzer, Siemens Healthcare Diagnostics, Germany) using blood samples collected half an hour before morning administration. In addition to tacrolimus, most patients received a purine inhibitor that was either mycophenolate mofetil (n= 58) or azathioprine (n= 4).

Biological markers such as albumin (Alb, g/L), hemoglobin (Hb) (g/L), tacrolimus trough concentrations (ng/ml) and tacrolimus daily doses (mg/d) were recorded at different point time after transplantation for this study. Tacrolimus dose-adjusted trough concentration (C/D ratio) was calculated as trough concentration divided by the corresponding weight-adjusted daily dose (mg/kg/d). Clinical characteristics of the patients are shown in Table 1.

2.2. Genomic DNA isolation and genotype determination

DNA was isolated from peripheral white blood cells by Maxwell® 16 Genomic DNA Purification Kit.

The *CYP3A5* c. *6986A>G* polymorphism was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. PCR amplification was performed for a final volume of 21 µl containing 2mM of $MgCl_2$, 200 µM of d'NTP, 2U taq polymerase, 0.5 µM of each primer (forward: 5'-CATCAGTTAGTAGACAGATGA-3'; reverse: 5'-GGTCCAAACAGGGAAGAAATA-3') [8] and 30–80 ng of genomic DNA. The PCR conditions consisted of initial denaturation at 94°C during 3 minutes followed by 33 cycles with denaturation for 15 seconds at 94°C, annealing for 30 seconds at 55°C, extension for 40 seconds at 72°C, and a final extension at 72°C during 5 minutes. RFLP was performed at 37°C, overnight, using SspI (TAKARA Biotechnologie (Dalian) CO., LTD). Individuals with the AA genotype presented 3 fragments of 148 base pairs (bp), 125pb and 50pb, whereas individuals with the TT genotype presented 2 fragments of 198 pb and 125pb.

Genotyping of the The *ABCB1* c. *3435C>T* polymorphism was determined according to the methods described elsewhere[13], using primers 5′GATGTCTTGTGGGAGAGGGA3′ (forward) and 5′GCATGTATGTTGGCCTCCTT3′ (reverse). The PCR product of 451 bp was digested with MboI (TAKARA Biotechnologie (Dalian) CO., LTD), resulting in fragments of 245, 172 and 34 bp for the C allele, and 245 and 206 bp for the T allele [9].

2.3. Statistical analysis

The data were described as mean ± standard deviation or number (%). The distribution of mean with ± standard Analysis of Variance (ANOVA) Calculator [10]. For each polymorphism (SNP), the patients were classified into 3 groups: wild homozygotes, heterozygotes and homozygotes variants. All statistical analyses were performed with Epi-InfoTM version 7 software. The odds ratios (OR) and 95 % confidence interval (CI) were determined with logistic regression analysis. A p value <0 .05 was considered as statistically significant.

4. Results

4.1. Clinical characteristics distribution

The clinical characteristics of 63 kidney recipients transplant patients at deferens time points are presented in Table 1. Our results showed that, there was a difference distribution for the level of hematocrit, hemoglobin, urea, glycerine, bilirubin, Tac dose, Tac concentration and Tac Concentration/Dose Ratio.

4.2. The CYP3A5 c. 6986A>G and ABCB1 c. 3435C>T polymorphisms distribution and Tac pharmacokinetic

In table 2, the *CYP3A5 c. 6986A>G* and *ABCB1 c. 3435C>T* polymorphisms distribution were reported for the Tac dose, Tac concentration and Tac concentration/Tac dose ratio. There was a significant difference in distribution of TAC Concentration/Dose Ratio observed in Days 30 to 90 between different genotypes of the *CYP3A5 c. 6986A>G* and *ABCB1 c. 3435C>T* polymorphisms. At one year, the Tac dose and Tac Concentration/Dose Ratio presents a significant difference distribution for only the *CYP3A5 c. 6986A>G* genotypes.

4.3. Impact of the CYP3A5 c. 6986A>G and ABCB1 c. 3435C>T polymorphisms on Tac optimal concentration

The table 3 present the genotypes and allelic distribution of the *CYP3A5* rs776746 and *ABCB1* rs1045642 polymorphisms in two groups of Algerian renal transplant recipients patients (with and without the Tac optimal concentration). We considerate that the Tac concentration as optimal if there is between 3 and 7 ng/ml.

We found that, these two polymorphisms in Algerian renal transplant recipients patients do not influence the Tac optimal concentration.

Table 1: Demographics. clinical characteristics of the Algerian renal transplant recipients.

	Days 1 to 15 n= 28	Days 15 to 30 n= 28	Days 30 to 90 n= 28	Days 90 to 180 n= 33	1 year n= 63	*P value*
Age (years) (means ±SD)	31.25 ± 7.73	31.25 ± 7.73	31.25 ± 7.73	30.6 ± 7.57	32.16 ±10.50	0.9
Gender (male/female)	20/8	20/8	20/8	22/11	46/17	
Hematocrit (means ±SD)	27.01 ± 16.1	31.07± 7.16	37.21± 13.51	42± 5.76	40.47± 5.95	**0.0001**
Hemoglobin (means ±SD)	9.22± 2.69	10.97± 1.7	12.49± 3.55	13.03± 2.07	13.24± 1.84	**0.0001**
Albumin (means ±SD)	37.92 ± 53.74	40.28± 8.07	42.82± 6.63	45.56± 6.03	44.42± 5.75	0.6
Ure (means ±SD)	0.71 ± 0.17	0.45± 0.15	0.39± 0.25	0.11± 0.39	0.43± 0.24	**0.0001**
Creatine (means ±SD)	16.3 ± 9.94	13.77± 5.24	13.19± 3.2	13.58± 4.72	13.93± 4.57	0.2
Uric Acid (means ±SD)	56.28 ± 18.98	58.14± 23.55	51.16± 9.6	58.79± 12.7	59.37± 13.28	0.2
GOT (means ±SD)	25.04 ± 17.9	26.59± 22.05	22.93± 18.93	19.31± 12.1	23.04± 9.12	0.4
GPT (means ±SD)	29.7 ± 30.47	22.11± 10.87	19.94± 12.4	19.72± 9.83	21.44± 11.21	0.1
BIL (means ±SD)	4.43 ± 2.2	4.13± 1.66	4.65± 2.10	4.48± 1.9	5.54± 2.31	**0.01**
GG (means ±SD)	63.64± 17.75	70.45± 21.40	74.26± 17.27	77.7± 20.8	75.89± 21.88	0.05
MDRD (means ±SD)	58.61 ± 20.56	67.28± 24.48	66.46± 15.61	69.55± 22.52	64.20± 18.13	0.2
Glycemic (means ±SD)	1.05± 0.26	1.3± 1	0.96± 0.21	0.97± 0.27	0.91± 0.12	**0.03**
HBP (n)	19	19	19	24	43	
Diabetic (n)	11	11	11	11	12	
Hyperlipidemia (n)	9	9	9	12	17	
Tac dose (mg/day) (means ±SD)	0.14 ±	0.14± 0.05	0.096± 0.05	0.086± 0.04	0.056± 0.03	**0.001**
Tac concentration (ng/ml) (means ±SD)	10.24 ± 0.044.86	11.21± 5.9	7.5± 3.46	8.86± 3.94	6.49± 2.15	**0.001**
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg) (means ±SD)	79.39 ± 40.72	90.43± 57.46	143.8± 150.5	134.61± 96.95	146.7± 81.41	**0.04**

GOT: *Glutamic Oxaloacetic Transaminase.* ***GPT:*** *Glutamic-Pyruvic Transaminasen.* ***BIL:*** *Bilirubin.* ***HBP:*** *High Blood Pressure.* ***SD:*** *Standard Deviation.* ***n:*** *Number.* ***ng:*** *Nanogramme.* ***mg:*** *Milligram.* ***kg:*** *Kilogram.* ***Tac:*** *Tacrolimus.* ***ml:*** *Millilitre,* ***MDRD:*** *Modification of diet in renal disease.* ***CG:*** *Cockcroft-Gault,* ***P :****P value<0.05 is considerate as significant.*

Table 2: Demographics clinical characteristics of the Algerian renal transplant recipients and the distribution of the *CYP3A5* rs776746 and *ABCB1* rs1045642 polymorphisms

	CYP3A5 ****1/*1***	****1/*3***	****3/*3***	***P value***	***ABCB1*** **3435CC**	**3435CT**	**3435TT**	***P value***
days 1 to 15 (n=28)	**n=0**	**n= 24**	**n=4**		**n=14**	**n=3**	**n=11**	
Tac dose (mg/day)	0	0.144± 0.48	0.12 ± 0.028	0.9	0.15 ± 0.04	0.107± 0.01	0.13± 0.04	0.17
Tac concentration (ng/ml)	0	10.21 ± 5.09	10.52 ± 3.67	0.9	11.29± 5.72	11.2 ± 3.57	8.69± 3.78	0.4
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg)	0	73.37 ± 38.9	91.5 ± 55.62	0.4	76.59 ± 43.19	109.7± 52.8	74.68± 34.38	0.4
Days 15 to 30 (n=28)	**n=0**	**n= 24**	**n=4**		**n=14**	**n=3**	**n=11**	
Tac dose (mg/day)	0	0.13± 0.056	0.16± 0.07	0.3	0.14± 0.056	0.15± 0.1	0.12± 0.05	0.6
Tacconcentration (ng/ml)	0	10.05± 4.01	12.67± 7.85	0.3	9.7± 5.11	9.56± 3.12	11.57± 4.43	0.5
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg)	0	91.69± 59.19	83.13± 53.26	0.7	82.45± 63.76	68.47± 21.15	105.84± 55.91	0.4
Days 30 to 90 (n=28)	**n=0**	**n= 24**	**n=4**		**n=14**	**n=3**	**n=11**	
Tac dose (mg/day)	0	0.10± 0.05	0.05± 0.037	0.06	0.09± 0.058	0.06± 0.049	0.09± 0.046	0.6
Tac concentration (ng/ml)	0	9.05± 3.57	9.1± 1.98	0.9	9.21± 2.81	10.6± 1.58	9.24± 4.36	0.8
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg)	0	113.6± 7.39	309.9± 327.5	**0.003**	130.78± 89.17	346.3± 392.3	102.8± 52.16	**0.02**
Days 90 to 180 (n=33)	**n=0**	**n= 28**	**n=5**		**n=18**	**n=4**	**n=11**	
Tac dose (mg/day)	0	0.085± 0.04	0.09± 0.058	0.8	0.09± 0.052	0.06± 0.03	0.07± 0.03	0.3
Tac concentration (ng/ml)	0	8.95± 4.24	8.32± 2.46	0.7	10.06± 4.7	7.52± 3.51	7.37± 1.84	0.1
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg)	0	125.81± 65.87	183.85± 211.3	0.2	128.5± 71.49	188.94± 207.4	118.4± 60.6	0.4
1 year (n=83)	**n=0**	**n= 55**	**n=8**		**n=28**	**n=15**	**n=20**	
Tac dose (mg/day)	0	0.05± 0.03	0.05± 0.02	1	0.05± 0.02	0.04± 0.03	0.07± 0.03	**0.003**
Tac concentration (ng/ml)	0	6.50± 2.23	6.63± 1.77	0.8	6.63± 1.95	6.17± 2.46	6.4± 2.32	0.8
Tac Concentration/Dose Ratio (ng/ml)/(mg/kg)	0	144.9± 81.87	157.7± 96.7	0.6	152.2± 73	187.3± 108.3	112.82± 67.3	**0.03**

Tac : *Tacrolimus,* ***n :*** *Number. .* ***ng :*** *Nanogram,* ***Kg :*** *Kilogram,* ***mg*** *: Milligram,* ***ml :*** *Millilitre, Values presented as mean ± SD,* ***P :*** *P value<0.05 is considerate as significant.*

Table 3: Genotypes and allelic distribution of the *CYP3A5* rs776746 and *ABCB1* rs1045642 polymorphisms in Algerian renal transplant recipients between two groups (with and without the Tac optimal concentration).

At 1 year n=63	Tac c optimal n(%)	Tac c no-optimal n(%)	OR(95%CI)	P value
***CYP3A5* rs776746**				
Genotypes	**N=48**	**N= 15**		
*1/*1	0 (0)	0 (0)		
*1/*3	44 (69.8)	13 (20.6)	1	
*3/*3	4 (6.3)	2 (3.1)	1,63(0,13-13,31)	0,62
Alleles				
*1	44 (34.9)	13 (10.3)	1	
*3	52 (41.2)	17 (13.49)	1,10 (0,48-2,52)	0,81
***ABCB1* rs1045642**				
Genotypes	**N=48**	**N= 15**		
3435CC	21 (33.3)	8 (12.6)	1	
3435CT	12 (19.04)	3 (4.7)	0,65(0,09-3,48)	0,72
3435TT	15 (23.8)	4 (6.3)	0,70(0,13-3,25)	0,74
Alleles				
3435C	54 (42.8)	19 (15.07)	1	
3435T	42 (33.3)	11 (8.7)	0,74(0, 31-1,73)	0,49

Tac c : *Tacrolimus concentration* ***, % :*** *Parentage,* ***n :*** *Number* ***, P :*** *P value<0.05 is considerate as significant.,* ***OR:*** *Odd Ratio.*

Discussions

Since twenty two years ago, the tacrolimuse (Tac) has been the most used worldwide immunosuppressant treatment to prevent of allograft rejection [11]. In the present investigation, we have explored the impact of *CYP3A5* c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms on the Tac pharmacokinetic in sixty two kidney recipients transplant patients From West Algerian population.

Firstly, we analyzed the clinical data characteristics distribution at different time points. Secondly, we compared Tac dose, Tac concentration and the Tac concentration/Tac dose ratio between different genotypes of CYP3A5 c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms. Finally, we found that, these two polymorphisms in Algerian renal transplant recipients' patients do not influence the Tac optimal concentration.

On another hand we observed a different significant in distribution of Tac Concentration/Dose Ratio for *CYP3A5* c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms (Days 30 to 90) and of the Tac dose and Tac Concentration/Dose Ratio for only the *CYP3A5 c. 6986A>G* polymorphism.

Many studies have explored the impact of these polymorphisms in the Tac pharmacokinetic. Vannaprashat S *et al*, reported the same conclusion about *ABCB1* c. 3435C>T, these study demonstrated that there were no statistical significant different between Tac doses and maintenance phases and this polymorphism [12]. The same result was founded on Polish Caucasian kidney transplanted recipients [13]. In contrast, the *ABCB1* 3435 CC genotype in donor influences early renal function and creatinine recovery in Chinese tacrolimus-treated kidney transplant recipients [14]. However, the TT homozygotes at 3435 of *ABCB1* gene required a higher tacrolimus dose than those with wild alleles or heterozygote in Serbia kidney transplanted recipients patients [15].

Picard N *et al* study found the same results and showed that *CYP3A5* genotyping cannot help improve Tac therapy. Nevertheless a recent data have showed that weight adjustment daily dose of Tac required during introduction phase in kidney transplanted recipients patients who carried the genotype CYP3A5*1/*1 was higher than the CYP3A5*1/*3 and CYP3A5*3/*3 [16,17,18,19,20]. In Chinese population, the CYP3A5 6986A>G genetic polymorphism seems to affect daily dose requirements and concentration of Tac in kidney transplant recipients [21]. No data has been available in this regard from Moroccan or Tunisian populations.

The most important limitation of our study could be due to the small sample size. The in fact

sample size can influence the statistical power: as sample size is increased, power increases. It's imperative to increase the number of samples. In another hand, it seems important to explore these polymorphisms in DNA of kidney donors to explore they genotypes of *CYP3A5* c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms.

Conclusion and Perspectives

We have shown, for the first time in an Algerian population, that the *CYP3A5* c. 6986A>G and *ABCB1* c. *3435C>T* polymorphisms do not influence the Tac pharmacokinetic. On the other hand, it is important to explore other polymorphisms involved in the pharmacogenetic of Tac treatment that might be responsible of the variability of its pharmacokinetic as *CYP2A6* and *CYP3A4* genes.

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