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Abbreviations

AMR : antibody mediated rejection
C_0 : trough blood concentrations
CYP3A5 : cytochrome P450 3A5

Abstract

Pretransplantation adaptation of the daily dose of tacrolimus to *CYP3A5* genotype is associated with improved achievement of target trough concentration (C_0), but whether this improvement affects clinical outcomes is unknown. In the present study, we have evaluated the long-term clinical impact of the adaptation of initial tacrolimus dosing according to *CYP3A5* genotype: the transplantation outcomes of the 236 kidney transplant recipients included in the Tactique study were retrospectively investigated over a period of more than 5 years. In the Tactique study, patients were randomly assigned to receive tacrolimus at either a fixed dosage or a dosage determined by their genotype, and the primary efficacy end point was the proportion of patients for whom tacrolimus C_0 was within target range (10–15 ng/ml) at day 10. Our results indicate that the incidence of biopsy proven acute rejection and graft survival were similar between the control and the adapted tacrolimus dose groups, as well as between the patients who achieve the tacrolimus C_0 target ranges earlier. Parients death, cancer, cardiovascular events and infections were also similar, and renal function did not change. We conclude that optimization of initial tacrolimus dose using pharmacogenetic testing does not improve clinical outcomes.

Introduction

The calcineurin inhibitor tacrolimus is a key component of modern immunosuppression protocols in kidney transplantation (1). Together with its narrow therapeutic window, the great inter-individual variability in tacrolimus pharmacokinetic parameters are majors concerns, and the relationship between tacrolimus trough blood concentrations (C_0) with toxicity and rejection fostered the development of biomarkers that would help to individualize drug dosage in predicting the pharmacokinetic responses *(2, 3).* Numerous intrinsic and extrinsic parameters influence tacrolimus pharmacokinetic parameters, and variations in the expression and/or activity of drug metabolizing enzymes and transporters, in general supported by single nucleotide variants (SNVs), received much attention over the 15 last years (4). Of particular importance is the impact of variants in the genes encoding P450 cytochromes 3A (*CYP3A4* and *3A5*), which control tacrolimus hepatic metabolism and intestinal absorption, in tacrolimus pharmacokinetic profiles (5, 6), and a large body of evidence has validated the effects mediated by the SNV at position 6986 of the *CYP3A5* gene (rs776746; 6986A>G) (7). This variant causes a splicing defect resulting in the absence of functional CYP3A5 protein (8). Patients who are homozygous for the 6986 G allele (designated as *CYP3A5*3*) are therefore expected to lack CYP3A5 activity and require higher tacrolimus dose to reach the target C_0 range.

The rationale for the adaptation of initial tacrolimus dose using pharmacogenetic testing of *CYP3A5* genotypes in kidney transplantation is supported by the theoretical risk of increased rejection episodes in patients who failed to reach therapeutic tacrolimus C_0 ranges early after transplantation, for example the *CYP3A5*1/*1* carriers (expressers) in whom higher dose requirement may cause a delay in reaching the desired C_0 (9-11) even though this concept has been recently challenged (12). Nevertheless, there is now a relative consensus on the fact that pharmacogenetic adaptation of the

daily dose of tacrolimus to *CYP3A5* genotype might improve achievement of the target C_0, but that this strategy actually fails to improve short-term (up to three months) transplantation outcomes, including rejection, delayed graft function and acute nephrotoxicity (7, 13).

The critical point that remains, and that has never been investigated, is whether genotyping kidney transplant candidates for *CYP3A5* variants improved the long-term clinical outcomes after transplantation, and this information is crucial for advocating the implementation of routine testing of *CYP3A5* in kidney transplantation. To address this issue, we have investigated the results of the Tactique study, which was initially undertaken to test whether pharmacogenetic adaptation of the daily dose of tacrolimus is associated with improved achievement of the target C_0 (14), over a period of more than 5 years.

Patients and methods

Study design

The Tactique study, a prospective and multicenter trial, was conducted in 2006 and 2007 to evaluate whether adaption of tacrolimus dosing according to the *CYP3A5* genotype would allow earlier achievement of tacrolimus C_0 in kidney transplant recipients. The design of the study is detailed in (14). Included patients were randomly assigned at day 7 post transplantation to receive tacrolimus at either a fixed dosage of 0.2 mg/kg/day (the control group, n=120) or a dosage determined by their genotype: CYP3A5 expressers (i.e., carriers of the *CYP3A5*1* allele) received 0.3 mg/kg/day, whereas CYP3A5 non-expressers (*CYP3A5*3/*3* genotype) received 0.15 mg/kg/day (the adapted-dose group, n=116). The first measurement of C_0 was performed after the intake of six doses (=day 10 after transplantation) and the primary efficacy end point was the proportion of patients for whom tacrolimus C_0 was within target range (10–15 mg/l) at day 10. All patients received a biological induction (16% basiliximab, 84% rabbit thymocyte antiglobulin), 3g of mycophenolate mofetil (Cell-Cept; Roche, Basel, Switzerland) daily for 15 days (tapered to 2 g/day) and a tapered corticosteroid regimen.

For the long-term follow-up study presented here, we investigated the medical records of all the patients analyzed on the basis of the intention-to-treat principle in the Tactique study, and for whom the graft and/or life status was available at the date of September 1, 2015. This information was lacking in 24 out of the 236 patients, which were excluded from the study. Research assistants within each center who participated to the initial Tactique study manually retrieved clinical and biological parameters. This study was approved by the institutional review board at each participating center, and written informed consent was obtained from all patients. The study was carried out in compliance with the provisions of the Declaration of Helsinki, and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Statistical analyses

Demographic and baseline characteristics were summarized as counts and percentages for categorical variables, and continuous variables as means$\pm$standard deviation.

To address the long-term outcome of the optimization of initial tacrolimus dose using pharmacogenetic testing on the basis of the Tactique study, we compared the primary and secondary end-points in groups according to (1) the randomization arm (ie. adapted versus control groups), and to (2) the success versus failure of the primary end point, which was the proportion of patients for whom tacrolimus C_0 was within target range (10–15 ng/ml) after six oral doses. Hence,

such comparisons would provide information of the clinical impact of adapting tacrolimus doses according to *CYP3A5* genotype, and determine whether reaching target tacrolimus C_0 range at an earlier time point after the transplant could improve graft outcomes.

The primary outcome of this follow-up study was the incidence of graft loss over time, which was estimated with Kaplan-Meier survival analysis, and compared between groups using the Log Rank test. Secondary end-points were clinical parameters including incidence of biopsy-proven acute rejection, patient death, cardiovascular events, cancers, and infections, and biological parameters including proteinuria, graft function, and hemoglobin A1c at the last follow-up visit. Categorical data were compared using Chi square test; continuous variables were compared using the Student's t-test. The incidences of graft loss and biopsy-proven graft rejection were estimated using Kaplan–Meier curves. All tests were two tailed, and a P value <0.05 was considered statistically significant. All analyses were performed using JMP.10.0.0 (SAS corporation).

Results

Patients demographics and baseline characteristics

The initial intention-to-treat population of the Tactique study was made of 236 individuals (120 in the control group, and 116 in the adapted dose group) (14). All patients from this population for who graft and/or living status were available at the date of September 1, 2015 were included for the present follow-up study, and 24 out of the 236 patients were lost to follow-up. Consequently, the final study population was made of 212 patients: 104 in the control group and 108 in the adapted dose group. The characteristics of this population of according to the randomization arms are detailed on the **Table 1.** The two groups of patients were comparable regarding the recipients and donors demographic and clinical characteristics. As expected, the proportion of patients who reached the primary end-point was still significantly higher in the adapted-dose group compared with the control group (42% versus 25%, p=0.01, Chi square test), indicating that the loss of patients in the follow-up study did not skew the study population.

Pharmacogenetic adaptation of the daily dose of tacrolimus does not impact rejection rates and graft survival.

To test whether pharmacogenetic adaptation to *CYP3A5* genotype of the daily dose of tacrolimus influences transplantation outcomes, we compared the incidence of kidney allograft loss over time between the control and the adapted groups. The Kaplan-Meier curves in the **Figures 1 A and B** indicate that graft survivals (including death-censored) are strictly comparable between the two groups of patients. Similarly, the incidence of biopsy-proven acute rejection was not different over time between the two groups (**Figure 1C**). Since the rate of success of the primary end-point was the only statistically different parameter between the two groups (**Table 1**), we also tested whether this parameter could impact graft survival and rejection incidence. Again, the incidence of graft loss and rejection among patients who reach tacrolimus C_0 target range earlier were similar to patients who did not (**Figure 1 D and E**).

Pharmacogenetic adaptation of the daily dose of tacrolimus does not impact graft outcomes

We next evaluated whether pharmacogenetic adaptation of the starting dose of tacrolimus after kidney transplantation provided better outcomes. The occurrence of adverse events related to renal transplantation, including cancers, infections and cardiovascular events in the study population was

in accordance with the literature (11). Indeed, the prevalence of cancer was 21%, infections 47%, and cardiovascular events 20%. Seventeen (8%) of the patients died during the follow-up period. We did not found any significant difference between the control group and the adapted tacrolimus dose group, in terms of death, cancer, infection and cardiovascular events (**Table 2**). In addition, there was no significant between-group difference regarding renal function, proteinuria or blood pressure (**Table 2**). Similarly, we found no difference between patients who reached tacrolimus C_0 target range earlier and patients who did not reach the tacrolimus C_0 range in terms of adverse events or renal function (**Table 3**).

Discussion

Our results indicate that, on the basis of the long-term follow-up of patients included in the Tactique study, tacrolimus dosage adaptation to *CYP3A5* does not improve graft survival, rejection rates and adverse events related to transplantation. Even if these results do not support routine testing for *CYP3A5* genotypes prior to transplantation, caution must be paid before generalizing them because of the specificities of the Tactique protocol that may not be representative of the usual kidney transplant donor/recipients characteristics. Indeed, patients included in this study were highly selected with no expanded criteria donors, and had a low immunological risk. Even if the immunosuppressive regiment was the standard (corticosteroids, mycophenolate mofetil and tacrolimus), the target tacrolimus C_0 were higher than those currently recommended, notwithstanding that the optimal C_0 ranges for preventing rejection are not defined (15, 16). Most of the patients received induction with thymoglobulin and high mycophenolate dosages, despite a low immunological risk (to allow the delay of the introduction of tacrolimus), which may participate in the low rejection rate (<10%) and the very good results in terms of graft survival in the whole cohort (90% at five years, 80% at nearly 10 years). Given the low occurrence rate of the primary outcome of this follow-up study (graft loss), one must acknowledge that a larger population would have been required to detect a small effect (if any) of tacrolimus adaptation to *CYP3A5* genotype on graft survival. Of the patients lost to follow-up there were twice as many (16) in the control group as in the adapted dose group (8), and the difference between proportions of patients achieving the primary end-point was greater in the follow-up cohort than in the primary study which can generate a potential survivorship bias. However, that would have been expected to bias in favor of a positive result. One other limitation is the relatively lower proportion of CYP3A5 expressers based on the ethnicity of the study population, and, it is possible the results might be different in a population with a higher number of CYP3A5 expressers.

The rationale for adapting tacrolimus dosage to *CYP3A5* genotype was based in the assumption that tacrolimus underexposure in the first days after transplantation increases the risk of acute cellular rejection, and that would be relevant for patients who express CYP3A5 (*CYP3A5*1/*1*) and require higher doses (10). In addition, tacrolimus overexposure would foster chronic nephrotoxicity (7). Nevertheless, these hypothesis have never been formally validated, and despite a large number of studies and meta-analysis having addressed the question, whether *CYP3A5* genotype constitute a risk factor for adverse graft outcomes is still awaiting confirmation (7, 13, 17). In a conceptual point-of-view, if a parameter, namely the *CYP3A5* expresser genotype, is not formally validated and universally accepted as a risk factor for adverse outcomes, there is no obvious reason for that efforts engaged to anticipate the effects of the presence of this risk factor in a population would succeed to improve the outcome.

If dosing tacrolimus based on *CYP3A5* genotype does not improve clinical outcomes, the rationale for pharmacogenetic testing in kidney transplantation must be re-assessed taking into account that kidney transplantation is an evolving field, with highly controversial paradigms, like the causes of graft loss, or the role (and the definition) of calcineurin inhibitors nephrotoxicity, for a few examples. Therefore, the risk factors for adverse outcomes are constantly remodeling, and we believe that the next developments in kidney transplantation epidemiology should support an integrative approach that would include demographic, clinical and biological parameters to generate risk scores and subpopulations of patients at risk, rather than focusing on a single parameter (18). We believe that pharmacogenetic markers could be integrated in this process, and should not only include *CYP3A5* variants, but also *CYP3A4*22*, perhaps *POR*28 (*P450 oxydoreducase) and *ABCB1* (ATP Binding Casette 1) (9). In addition, donor genotypes for *ABCB1* and *CYP3A5*, which impact calcineurin inhibitors nephrotoxicity, should also be taken into account (19, 20).

In general, selective pharmacogenetic markers are successfully incorporated into clinical practice if they are able to predict a potentially fatal side effect (for example dihydropyrimidine dehydrogenase gene variants and 5 fluorouracil toxicity (21)) or a clinical response (for example Kras mutations and response to cetixumab (22)) with a strong association with the genotype. Such genetic markers are not available for the immunosuppressive agents armamentarium used in clinical transplantation. A promising perspective for pharmacogenetic testing implementation in clinical transplantation could be the identification of drug-response markers of antibody-mediated rejection treatments, to rationalize the cost-effectiveness of the treatments.

In conclusion, we have provided evidence that initial dosing of dosing tacrolimus based on *CYP3A5* genotype prior to transplantation does not improve clinical outcomes over the long term. Pharmacogenetic testing in kidney transplantation should be reconsidered in the light of the profound changes that operated in the last ten years in the way we understand the pathophysiology of allograft nephropathy, in the development of the immunosuppressive agents targeting AMR, and in the development of integrative epidemiology for assessing transplantation outcomes.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure legend

Figure 1: Impact of pharmacogenetic adaptation of the daily dose of tacrolimus on rejection rates and graft survival. (A) Kaplan–Meier survival curves for the association between control and adapted tacrolimus doses groups at different time points after transplantation and graft survival in the cohort of 212 patients. (B) Kaplan–Meier death censored survival curves for the association between control and adapted tacrolimus doses groups at different time points after transplantation and graft survival in the cohort of 212 patients. (C) Kaplan–

Meier survival curves for the association between control and adapted tacrolimus doses groups at different time points after transplantation and the incidence of biopsy-proven acute cellular rejection (BPAR) in the cohort of 212 patients. (D) Kaplan–Meier survival curves for the association between patients who reached or not the primary endpoint of the Tactique study at different time points after transplantation and graft survival in the cohort of 212 patients. (E) Kaplan–Meier death censored survival curves for the association between patients who reached or not the primary endpoint of the Tactique study at different time points after transplantation and graft survival in the cohort of 212 patients.

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Table 1. Recipients and donors baseline characteristics

Continuous variables are presented as mean±standard deviation; nominal variables are presented as n and percentage

	Control group (n=104)	**Adapted dose group** (n=108)	**P value**
Age of recipient (years)	45±1.2	47±1.2	0.2
Male recipient-n(%)	74 (71)	71 (65)	0.7
Caucasian origin-n(%)	77 (90)	77 (88)	0.8
Initial Renal disease diagnosis-n(%)			0.6
Cystic	20 (19)	25 (23)	
Diabetes	4 (3)	3 (3.5)	
Glomerulonephritis	33 (32)	31 (29)	
Hypertension	10 (9.5)	9 (8.5)	
Interstitial nephritis	13 (13)	9 (8.5)	
Other/unknown	24 (23)	33 (30)	
Donor age (years)¶	46.7±1.3	46.7±1.3	0.9
Donor male sex-n(%)	67 (65)	64 (60)	0.3
Previous transplantation-n(%)	6 (6)	6 (5.5)	0.9
Cause of death			0.4
Trauma	33 (34)	35 (34)	
Cerebrovascular event	48 (49)	43 (42)	
Other	16 (16)	24 (23)	
Cold ischemia time (hrs)	15.6±0.6	15.8±0.6	0.7
CYP3A5 genotype			0.4
1/1	6 (5.5)	4 (3.5)	
1/3	15 (14.5)	22 (20)	
3/3	83 (80)	82 (75)	
Primary end point success*-n(%)	26 (25)	46 (42)	0.01

* Tacrolimus C_o within the target range of concentration [10-15ng/mL] 10 days after transplantation

¶ Only deceased donors.

Table 2. Study secondary end points according to the randomization arm

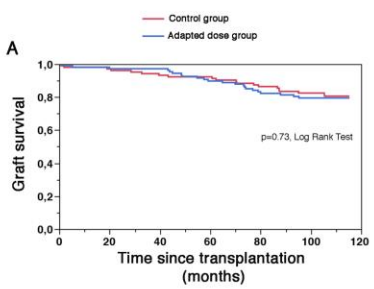
Continuous variables are presented as mean±standard deviation; nominal variables are presented as n and percentage

	Control group (n=104)	**Adapted dose group** (n=108)	**P value**
Events			
Death-n(%)	6 (6)	11 (10)	0.2
Cancer-n(%)	15 (20)	17 (21)	0.8
Infection-n(%)	41 (55)	45 (50)	0.5
Cardiovascular events-n(%)	13 (17)	16 (20)	0.6
De novo donor specific antibodies-n(%)	15 (15)	23 (22)	0.2
Last follow-up visit			
Time after transplantation (months)	80±2.4	85±2.3	0.15
Weight (kg)	84±5.2	74±5	0.9
Systolic blood pressure (mmHg)	136±2	135±2	0.6
Diastolic blood pressure (mmHg)	79±1	78±1	0.6
Tacrolimus C_0/dose (ng/ml)/(mg)	1.5±0.2	1.6±0.3	0.15
Serum creatinine (µmol/l)	172±19	175±18	0.9
Hemoglobin A1c (%)	5.7±0.15	6.2±0.15	0.06
Proteinuria (g/l)	0.7±0.1	0.7±0.1	0.8

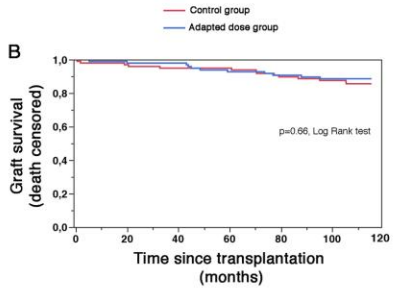
Table 3. Study secondary end points according to the primary end point of the Tactique study
Continuous variables are presented as mean±standard deviation; nominal variables are presented as n and percentage

	Success group (n=73)	**Failure group** (n=139)	**P value**
Events			
Death-n(%)	5 (7)	12 (8)	0.6
Cancer-n(%)	10 (19)	20 (22)	0.7
Infection-n(%)	55 (53)	26 (50)	0.5
Cardiovascular events-n(%)	11 (21)	18 (17)	0.6
De novo donor specific antibodies-n(%)	26 (20)	12 (17)	0.6
Last follow-up visit			
Time after transplantation (months)	83±2	82±2	0.6
Weight (kg)	74.3±6	81.9±4	0.3
Systolic blood pressure (mmHg)	138±2	134±1	0.2
Diastolic blood pressure (mmHg)	81±1	79±1	0.5
Tacrolimus C_0/dose (ng/ml)/(mg)	1.4±0.2	1.6±0.1	0.3
Serum creatinine (μmol/l)	156±22	183±16	0.3
Hemoglobin A1c (%)	6±0.1	5.6±0.1	0.06
Proteinuria (g/l)	0.9±0.2	0.6±0.1	0.8

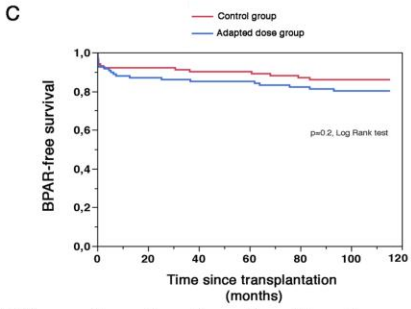
FIGURE 1



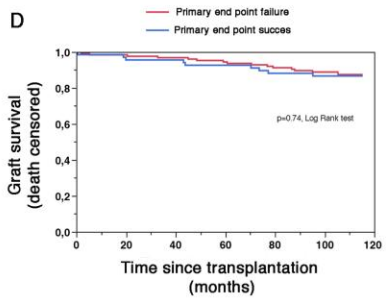
At risk, control group	104	102	98	94	89	76
At risk, adapted dose group	108	106	106	97	89	76



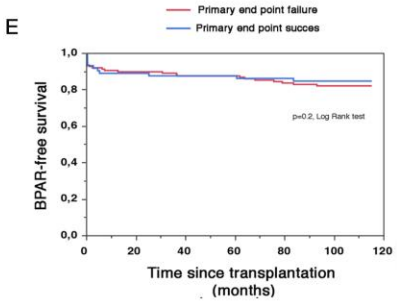
At risk, control group	98	95	94	91	87	77
At risk, adapted dose group	97	96	95	90	88	76



At risk, control group	101	94	90	87	85	75
At risk, adapted dose group	107	94	92	89	84	76



At risk, success group	68	66	65	63	60	52
At risk, failure group	127	125	125	118	115	98



At risk, control group	101	94	90	87	85	75
At risk, adapted dose group	107	94	92	89	84	76