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Influence of age and sex on pharmacokinetics of tacrolimus in post renal transplant patients- A single center experience

[1]Paulin A. Gandhi, [2]Aruna V. Vanikar ,[1]Rashmi D. Patel, [1]Kamal V. Kanodia, [1]Kamlesh S. Suthar, [1]Lovelesh A. Nigam, [3]Himanshu V. Patel

[1]Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology. G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre (IKDRC) - Dr. H.L. Trivedi Institute of Transplantation Sciences (ITS)

[2]Department of Regenerative Medicine and Stem Cell Therapy. G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre (IKDRC)- Dr. H.L. Trivedi Institute of Transplantation Sciences (ITS)

[3]Department of Nephrology and Transplantation Medicine. G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre (IKDRC)- Dr. H.L. Trivedi Institute of Transplantation Sciences (ITS)

Corresponding Author: Dr. Paulin A. Gandhi , Assistant Professor, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi And K.M. Mehta Institute of Kidney Diseases & Research Centre (IKDRCITS)- Dr. H.L. Trivedi Institute of Transplantation Sciences (ITS), Civil Hospital Campus, Asarwa, Ahmedabad- 380016, Gujarat, India.

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Abstract

Aim: Our study was aimed to evaluate the effect of age and gender on pharmacokinetics of tacrolimus drug in post-renal transplant (RT).

Material and Methods: This was a retrospective single center study carried out on 250 post- RT patients with mean age of 37.39±11.7 years, from October'17 to January'19 at IKDRC-ITS, Ahmedabad to evaluate effect of age and gender on trough blood tacrolimus level in Post-RT patients. Study population was divided in Group-1 and Group-2 taking tacrolimus dosage of 0.02-0.03 mg/kg and 0.04-0.05 mg/kg of body weight, respectively and blood tacrolimus was measured.

Results: A highly significant difference was observed in value of tacrolimus between age group of <30 years and 30-50 years ($p<0.01$) but no significant difference was found in 30-50 years age group and >50 years age group ($p>0.05$). When we compared value between <30 years and >50 years of age, the value was high in >50 years subgroup but it was statistically insignificant ($p>0.05$). Similar findings were noted in Group-2 as Group-1 for same age sub-groups. On analysis of influence of gender on trough tacrolimus level, females displayed lower levels but these were statistically insignificant ($p>0.05$).

Conclusion: TDM of tacrolimus is affected by age and gender. It gets metabolized more efficiently in patients younger than 30 years and in females in comparison to patients aged >30 years and males respectively. Thus while deciding dosage of tacrolimus for post-RT patient, age and gender must be considered as an important factor to achieve appropriate level and thereby better outcome.

Keywords: Tacrolimus, Age, Gender, Renal Transplant, Pharmacokinetic

Introduction

Transplantation is now an established therapeutic modality for end organ failure. However since the transplanted tissue/ organ being foreign to the host immune system, gets rejected by the host. Thus the main goal in solid organ transplantation (SOT) is to achieve maximum therapeutic effect of an immunosuppressant so that long term stable graft function is maintained and there are minimum/ no adverse events. Tacrolimus has emerged as a highly effective and valuable therapeutic alternative to cyclosporine in SOT especially in post renal transplant (RT) patients. With the introduction of new drug, new challenges have arisen to perform proper therapeutic drug monitoring (TDM). TDM of tacrolimus is crucial part of RT because of its narrow therapeutic window and high inter/intra-individual variability. In post-RT patients, both sub-therapeutic and supra-therapeutic drug concentration can have devastating effects. Sub-therapeutic level may lead to transplant rejection and on other side supra-therapeutic level leads to adverse effects like nephrotoxicity, neurotoxicity, hypertension, infections, and lymphoproliferative disorders.[1] Tacrolimus shows high inter/intra-individual variability due to multifactorial reasons like hepatic dysfunction, hepatitis C infection status, time after transplantation, patient age, gender, donor-recipient age/ size mismatch, recipient race, hematocrit and albumin concentration, diurnal rhythm, food administration, corticosteroid dosage, cytochrome P450 (CYP) isoenzyme and P-glycoprotein expression.[2] All these factors can affect tacrolimus concentration up to 100 fold in individual patients.

Recipient age is one of the factors which alter the pharmacokinetics of tacrolimus. Inter/intra- individual effect of tacrolimus primarily appears because of the effect of age on activity of CYP3A5 and its genotype. Age related alteration in drug metabolism and changes in hepatic blood flow, liver span, and its drug binding/ distribution capacity are well known however the exact reason is unknown.[3, 4]

Tacrolimus metabolism is also varying in males and females. This variation is probably due to mild or moderately faster activity of CYP3A in women compared to men, although clearance of p-glycoprotein substrates appear to be similar in men and women.[5]

We have carried out this study to evaluate the effect of age and sex on trough blood tacrolimus level in a cohort of post RT patients.

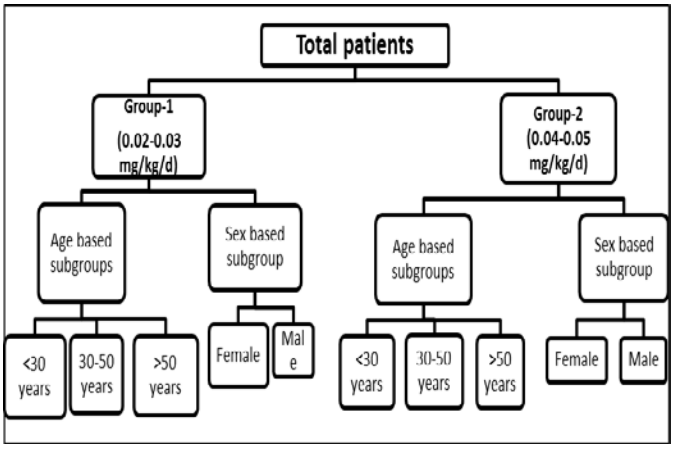
Material and methods

This was a prospective single center clinical study approved by Institutional Review Board, to observe the effect of age and sex on pharmacokinetics of tacrolimus in post-RT patients. Study period was from October'17 to January'19.

Study design:

All patients were primarily divided in two groups on the basis of daily dosage, group-1 included patients receiving tacrolimus, 0.02-0.03 mg/kg/day and group-2 included patients receiving tacrolimus, 0.04-0.05 mg/kg/day. Both groups were further sub-grouped according to age and sex. For studying the effect of age,

they were further subdivided in to three groups, namely <30 years, between 30 years to 50 years and > 50 years in both the groups. Details of group distribution are shown in flow chart.



Inclusion criteria were all post RT patients aged ≥ 18 years, belonging to any sex. Patients with any liver disease, sero-positivity for HIV, HbSAg, HCV, taking other medications altering tacrolimus metabolism significantly like Azole, Fluroquinolones, Sirolimus, Rifampin and Isoniazid were excluded.

Venous blood samples were collected after 12 hours of tacrolimus administration and before the next dose administration, in EDTA vacutainer. Whole blood was analyzed in Fully Automated Biochemistry Analyzer (Siemens, RxL Dimension, Germany) by Affinity Chromatography Micro-enzyme Immuno Assay (ACMIA) method. ACMIA is a technique in which free and antibody-bound antibody-enzyme-conjugate is separated using magnetic particles. The instrument mixes and sonicates an aliquot of whole blood followed by incubation with an anti-drug antibody conjugated to β-galactosidase. Drug-coated magnetic beads are used to remove unbound conjugate and the concentration of drug in the sample is measured spectrophotometrically after hydrolysis of substrate by β-galactosidase. After measurement, effect of age and sex on blood tacrolimus level was analyzed in both the groups.[6]

Statistical Analysis

All values were expressed as mean ± SD. Comparison of results was made with student's unpaired-t test for different age groups and for male and female sex. Correlation was calculated with Pearson correlation coefficient using GraphPad Instat version 3.03 statistical software; p value < 0.05 was considered as statistically significant.

Results

Totally 250 patients, 198 males and 52 females with mean age, 37.39 ± 11.7 years were enrolled for the study. Group-1 included 147 patients (M:F, 119:28), with mean age of 38.65 ± 13.2 years; group-2 included 103 patients (M:F, 81:22), with mean age of 35.6 ± 8.8 years. No age and sex bias was observed between both groups (p>0.05).

A highly significant difference was observed in value of tacrolimus between age group of <30 years and 30-50 years but no significant difference was found in 30-50 years age group and > 50 years age group. When we compared value between <30 years and >50 years of age, the mean value was high in > 50 years subgroup, however it was not statistically significant. When we analyzed tacrolimus level in group-2 for same age sub-groups, similar observations were noted as in group-1. There was significant difference between <30 years and 30-50 years, but no significant difference was noted between 30-50 years age group and >50 years age group, as well as between <30 years age group and >50 years age group. Comparison of Mean and standard deviation (SD) in both the groups is shown in **Table-1**, and **Table-2.**

On analysis of effect of sex on trough tacrolimus level, although females displayed lower levels, these were not statistically significant. Values are displayed in **Table-3.**

Discussion

Calcineurin inhibitor (CNI) tacrolimus remains the backbone of immunosuppression for post-RT patients; however protocols yielding effective results vis a vis minimal toxicity are yet to emerge. The main problem is due to influence of many factors on its pharmacokinetics. Tacrolimus is extensively metabolized by CYP3A isoenzymes (a member of cytochrome p450 family) and p-glycoprotein in the liver and intestine which generate different metabolites like demethyl-, demethylhydroxy-, didemethyl-, didemethylhydroxy- and hydroxy-tacrolimus with different efficacy.[7,8] CYP3A and p-glycoprotein are greatly affected by several factors like concomitant drug administration, age, sex, liver function status, post-RT duration, and all of these synergistically produce inter-individual variation[2]. All these factors and complexity in tacrolimus metabolism are required to be studied to minimize the adverse effect and bring upon a better outcome.

In this study, we evaluated effect of age and sex on pharmacokinetics of trough tacrolimus level in post-RT patients. We observed that age group of 18-30 years had low values in comparison to age group > 30 years although the dosage was same. Saskia N. de Wildt et al. studied effect of age on 48 pediatric post-RT patients and reported that children younger than 5 years required higher dosage than elder children possibly due to age-related differences in drug disposition such as CYP3A4/5 metabolism and p-glycoprotein transport, volume of distribution, protein and erythrocyte binding, or renal function. [9, 10] Our finding is also supported by Stratta P et al., who studied interactions of age, sex, body mass index, genetics, and steroid with tacrolimus dosing in 450 post-RT patients. They concluded that patients >60 years of age were slow metabolizers of tacrolimus, possibly due to age related effect on absorption, metabolism and excretion of the drug.[11] Wrighton SA et al. studied the CYP3A4 content in the hepatic tissue and concluded that there was very low activity present in the fetus and it increased rapidly after birth to achieve the activity of almost 1.2 times higher than adults.[12] Our findings are also supported by study of Hunt C. et al who hypothesized that age related change in drug level was possibly due to changes in the liver blood flow, size or drug binding and distribution with advancing age, and not due to change in the activity of CYP3A.[3] Miura M et al. studied the effect of age on 110 post-RT patients, including 12 elderly patients > 60 years of age, 57 middle-aged patients between 40 and 59 years and 41 young adult patients 20 to 39 years of age, and concluded that aging process itself may have a small effect on the pharmacokinetics of tacrolimus.[13] Gabardi Steven et al. published study on pharmacokinetics of maintenance immunosuppressant in elderly patients and proposed that there were physiologic changes associated with age that can significantly affect pharmacokinetics of the maintenance immunosuppressive agents like tacrolimus.[14] Amitava Dasgupta et al. explained that age related changes in tacrolimus level was possibly due to differences in expression of CYP3A and alteration in bowel length, hepatic blood flow and P-glycoprotein expression with advancing age.[6] Shishido et al. demonstrated that pediatric renal transplant recipients require 2 to 4 fold higher doses of tacrolimus than adults to maintain similar trough concentrations.[4] However, further studies on larger population size are required to study the impact of aging on CYP and P-glycoprotein activity and expression, and also its effect on TDM of tacrolimus.

Gender is also an important factor to be studied for appropriate TDM of tacrolimus since gender also affects the pharmacokinetics of tacrolimus significantly. We found females had low level of blood tacrolimus level as compared to males. This was possibly due to higher activity of CYP3A in females compared to males. [15] Bing Zhu et al. studied the distribution and gender differences of CYP3A activity in Chinese subjects and concluded female subjects had higher activity of CYP3A than males and CYP3A is the major contributor to tacrolimus metabolism.[5] Hunt et al. showed that CYP3A activity was 24% higher in female recipients than males.[16] Fitzsimmons WE reported that there was no sex-specific effects on the pharmacokinetic of tacrolimus which was against our findings.[17] Velickovic-Radovanovic et al. also evaluated effect of gender in 20 Serbian kidney transplant recipients (10 men:10 women) on tacrolimus level and showed that there was remarkable inter-individual variation along with significant lower values in female patients. [18]

Limitations of the present study: We could not perform CYP3A and p-glycoprotein genotype study or could not measure their activity.

Conclusion

To conclude, TDM of tacrolimus is affected by age and gender. It gets metabolized more efficiently in patients younger than 30 years and in females in comparison to patients aged > 30 years and males respectively. Thus while deciding dosage of tacrolimus for post-RT patient, age and gender must be considered as an important factor to achieve appropriate level and thereby better patient outcome.

Abbreviations

SOT-Solid Organ Transplantation

RT – Renal transplantation

TDM- Therapeutic Drug Monitoring

CYP – Cytochrome P

HIV-Human immunodeficiency virus

HbsAg- Hepatitis B surface Antigen

HCV-Hepatitis C virus

EDTA-Ethel

ACMIA – Affinity Chromatography Micro-Particle Enzyme Immuno-assay

SD-Standard Deviation

CNI- Calcineurin Inhibitor

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Legends Table and figure

Table 1: Comparison of trough tacrolimus level with reference to age in group-1 (0.02-0.03 mg/kg)

Age-wise Subgroups (Years)	Tacrolimus level (ng/mL) (Mean ± SD)	Sub-Group comparison	p Value
<30 (n=47)	3.6 ± 3.0	<30 years and 30-50 years	P<0.01
30-50 (n=70)	6.3 ± 3.9	30-50 years and >50 years	P>0.05
C >50 (n=40)	4.4 ± 2.5	<30 years and >50 years	P>0.05

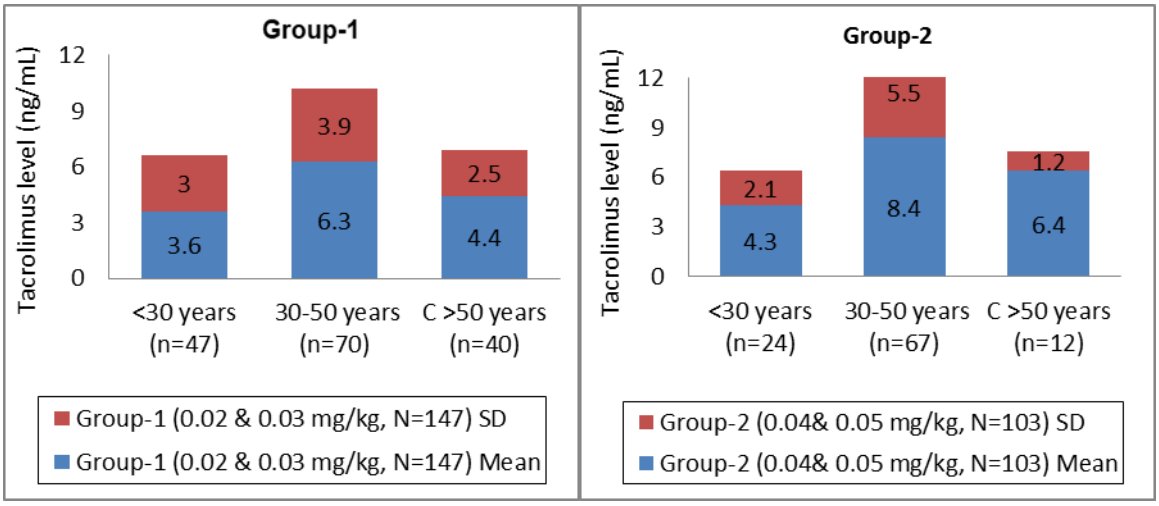
Table 2: Comparison of trough tacrolimus level with reference to age in group-2 (0.04-0.05 mg/kg)

Age-wise Subgroups (Years)	Tacrolimus level (ng/mL) (Mean ± SD)	Sub-Group comparison	p Value
<30 (n=24)	4.3 ± 2.1	<30 years and 30-50 years	P<0.01
30-50 (n=67)	8.4 ± 5.5	30-50 years and >50 years	P>0.05
C >50 (n=12)	6.4 ± 1.20	<30 years and >50 years	P>0.05

Table 3: Comparison of trough tacrolimus level between both genders in both groups

Gender-wise Subgroups	Group-1		Group-2	
	Mean ± SD	p Value	Mean ± SD	p Value
Male (n=200)	5.4 ± 3.7	P>0.05	7.5 ± 5.3	P>0.05
Female (n=50)	3.6 ± 2.8		7.0 ± 4.8	

Graph 1: Comparison of Mean and SD of blood tacrolimus level in both the groups within different age sub-groups



Graph 2: Comparison of Mean and SD of blood tacrolimus level in both the groups between male and female