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Population Pharmacokinetic Analysis of Oral Tacrolimus in Patients with Glomerulonephritis

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Abstract

Objective: Tacrolimus as an immunosuppressant is used to treat for several types of glomerulonephritis. Narrow therapeutic window and huge interindividual variability of tacrolimus make it impossible to predict its serum level. Hence, the purpose of this study was to derive population pharmacokinetic model for tacrolimus in glomerulonephritis patients.

Materials and methods: Adult patients diagnosed with glomerulonephritis and treated with oral tacrolimus were included. Electronic medical records were reviewed retrospectively to access clinical findings and demographic data. Population pharmacokinetics of tacrolimus was evaluated using non-linear mixed effect model by first-order conditional estimation with interaction algorithm.

Results: One hundred and forty-five patients were included in this study and one thousand and nine hundreds thirty-eight blood samples were analyzed. The estimated apparent clearance (CL/F) was 19.5 L/h, and apparent volume of distribution (V/F) was 380 L. The final model suggested that serum creatinine levels were negatively correlated with both CL/F and V/F whereas serum albumin levels were positively associated with V/F.

Conclusion: Various factors affecting tacrolimus pharmacokinetics were explored. The findings of this study pointed out that tacrolimus pharmacokinetics were related to patients' kidney function and serum albumin level in glomerulonephritis patients. Developed model may guide individualized tacrolimus therapy in glomerulonephritis patients and improve therapeutic outcomes in glomerulonephritis patients.

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Introduction

Glomerulonephritis (GN) is a group of renal disease that injures glomeruli, with the first step of filtering blood to produce urine [1]. Many patients with glomerulonephritis have mild, asymptomatic illness that is not noticed by patients and thus, remained undiagnosed [2]. Unfortunately, most of the patients possess risks of kidney failure and premature cardiovascular disease [3]. It is the third most common reason that patients lose their kidney function in South Korea [4]. In U.S., about 23% of the patients with end-stage renal disease lost their renal function as a result of GN [5]. The socio-economic burden of GN is enormous in its contribution to kidney failure requiring dialysis. Moreover, medical expenditure for GN tends to be higher than the one for diabetic nephropathy since it occurs earlier in life and most patients with GN live longer compared to patients with diabetic nephropathy [6].

Treatment of GN usually depends on types of GN and the severity of illness. Although the etiology of this disease is not precisely known, immunosuppressants are commonly used because many types of GN are believed to be immune disorders. Tacrolimus and cyclosporine, called calcineurin inhibitors, are one of these immunosuppressants. According to clinical practice guideline for GN published by KDIGO (Kidney Disease Improving Global Outcomes), tacrolimus is recommended to treat several types of GN such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), idiopathic membranous nephropathy (IMN), and Lupus nephritis [7,8]. For all these indications, KDIGO recommends serum level of tacrolimus needs to be regularly monitored to avoid toxicity and maintain efficacy because of its narrow therapeutic window [8, 9]. The problem is that maintaining tacrolimus serum level is tough. The pharmacokinetics of tacrolimus shows huge interindividual variability and various factors including drug interactions are all affecting tacrolimus pharmacokinetics [10]. That is why it has extensively studied in organ transplant population. Han NY, et al. demonstrated that hematocrit level, CYP3A5 genotype, and postoperative days were all influencing the clearance of tacrolimus. The authors also found body weight was associated with the volume of distribution (Vd) of tacrolimus in South Korean [11]. Population pharmacokinetics of tacrolimus in hematopoietic cell transplant (HCT) patients was also studied recently [12]. However, it was not studied in patients with GN patients.

Studying pharmacokinetics of tacrolimus in GN is important in that it is expected to be different from transplant population. The absorption of medications in chronic kidney disease (CKD) will be delayed due to decreased gastric emptying time and prolonged elimination half-life of the drug [13,14]. Distribution of the medication will also be affected by renal dysfunction. Many GN patients have low albumin level due to heavy proteinuria. As a result, hypoalbuminemia changes protein binding of drugs and increases the serum concentration of the free drug. Anemia is another factor that leads to pharmacokinetic changes. Since tacrolimus largely binds to erythrocytes, anemia of CKD may cause the alteration in tacrolimus pharmacokinetics [15]. Edematous status caused by proteinuria also alters the Vd of the drug [16,17].

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There are a few studies regarding population pharmacokinetics of cyclosporine or mycophenolic acid in patients with GN [18, 19]. However, none of them studied the pharmacokinetics of tacrolimus in GN. Due to huge inter-individual and intra-individual variability, predicting therapeutic effect of tacrolimus may be difficult. The association between tacrolimus pharmacokinetics and various factors (i.e. edematous status, hypoalbuminemia, and concomitantly used medication that can cause pharmacokinetic drug interaction with tacrolimus) were not clearly understood. Understanding of pharmacokinetics of tacrolimus is clinically significant due to its narrow therapeutic index and dose-related toxicities. Therefore, the objective of this study is to derive population pharmacokinetic model of tacrolimus in GN patients with identifyingto identify covariates that may be related to tacrolimus pharmacokinetics. It will improve pharmacotherapy with tacrolimus in patients with GN.

Methods and Materials

Study design and population

This is a population pharmacokinetic analysis study using the data from electronic medical records (EMR). We included all patients who diagnosed with GN and treated with tacrolimus-based immunosuppressive regimen at ambulatory clinic of Seoul National University Hospital outpatient clinics in South Korea between Jan 01, 2000 and Oct 30, 2013. All patients administered tacrolimus orally as hard capsule formulations twice daily. Patients under 18 years old and who were not reached the steady state condition of tacrolimus were excluded from the analysis.

Data collection and variables

EMR data were reviewed retrospectively to access clinical records, demographic data, and medication profile during study period. Clinical data included protein/creatinine ratio (PCR) in urine, complete blood counts including white blood cell (WBC), hemoglobin (HEMO), hematocrit (HCT), and platelet (PLT), renal function as blood urea nitrogen (BUN) andserum creatinine (SCR), cholesterol (CHOL), total protein (TPRO), albumin (ALBU), uric acid (URIC), total bilirubin (TBIL), aspartate transaminase (AST), and alanine aminotransferase (ALT). Demographic data included gender (SEX), body weight in kilogram (BWT), patient's age (AGE), and types of GN by etiology (DZ).Generic names and dosages information of concomitantly used medications was collected about any known drugs that increase or decrease serum tacrolimus levels referenced by Micromedex®. Baseline characteristics and correlation analysis were performed by SPSS ver.19 (SPSS Inc., Chicago, Illinois, U.S.A.).All serum tacrolimus levels were trough concentrationsanalyzed by liquid chromatography-mass spectrometry using Quattro microTM API tandem mass spectrometer (Micromass, Manchester, UK). Before 2007, Microparticle enzyme immunoassay (IMX Tacrolimus II assay, Abbott Lab, IL, USA) was utilized for the analysis of tacrolimus levels.

Population pharmacokinetic analysis

The population pharmacokinetic analyses of tacrolimus were performed using non-linear mixed effect model (NONMEM®) software (version 7.2.0, ICON Development Solutions, Ellicott City, MD). Perl speaks NONMEM (version 3.5.3.), Xpose® (R package, version 4), and Pirana® (version 2.5.0) were additionally employed for model diagnostics and graphical presentation. The first-order conditional estimation algorithm with interaction (FOCE+INTER) was used throughout the analysis, considering interactions between pharmacokinetic parameters.

Structural model building

Both one-and two-compartment models with or without a lag time and first-order absorption and elimination were compared in this study [20-22]. Typical value of the absorption rate constant (Ka) could not be estimated because of the lack of concentration data in absorption and distribution phase. Therefore, Ka value was fixed at 4.5 h-1 which was previously reported in a study ofliver transplant patients [23]. Since the bioavailability of tacrolimus (F) could not be calculated in this analysis, tacrolimus clearance (CL) and apparent volume of distribution (V) were matched to CL/F and V/F, respectively. Interindividual variability of each parameter in structural model was estimated by an exponential error model using following equation:

$$P_i = \theta \times e^{\eta i} \quad (1)$$

Where P stands for a pharmacokinetic parameter, P_i means the individual value for P in the i^{th} individual, θ is the population mean value of P (i.e.,CL/F, V/F), and ηj implys an interindividual variability which is the difference between the observed and predicted value. Residual variability ε_{ij}(i^{th} individual, j^{th} concentration), the difference between the observed ($C_{(obs,ij)}$)and model-predicted concentration ($C_{(pred,ij)}$), was compared with additive, proportional, and exponential error model. Equations are as follows in order:

$$C_{obs,ij} = C_{pred,ij} + \varepsilon_{ij} \quad (2)$$

$$C_{obs,ij} = C_{pred,ij}(1 + \varepsilon_{ij}) \quad (3)$$

$$C_{obs,ij} = C_{pred,ij} \times Exp(\varepsilon_{ij}) \quad (4)$$

Random effect parameters as η and ε were all presumed to be randomly distributed with a mean of 0 and variances of ω2 and σ2, respectively. Each different pharmacokinetic models were tested, and the best structural model was selected based on the goodness-of-fit after a visual predictive check (VPC), objective function value (OFV)of estimated models, and physiologic plausibility of parameter estimates.

Covariates were searched to evaluate the influence of demographics (SEX, BWT, AGE, DZ), clinical factors (PCR, WBC, HEMO, HCT, PLT, BUN, SCR, CHOL, TPRO, ALBU, URIC, TBIL, AST, ALT), and concomitantly used medications (i.e.,prednisolone, omeprazole, nifedipine, rifampin, fluconazole, rosuvastatin, omega-3-fatty acid). For continuous covariates, following equationwas used to test the significance of the covariates:

$$P=\theta \times e^{(\theta covariate \times (covariate\text{-}mean\ value\ of\ covariate))} \quad (5)$$

The θ is population mean value of the pharmacokinetic parameter and $\theta_{covariate}$ is the estimated effect of the covariate on parameters such as CL/F or V/F. For categorical variables (SEX, DZ, whether concurrent medications use), following equations were used for covariate modeling:

$$P=\theta \text{ for reference covariate} \quad (6)$$

$$P=\theta \times e^{(\theta covariate)} \text{ for exploratory covariate} \quad (7)$$

The $\theta_{covariate}$ is the assessed fractional change in θ for the exploratory covariate. Covariates were selected throughout a stepwise procedure by forward addition and backward elimination. Likelihood ratio tests

were done by comparing differences in OFV between models. In forward addition step, covariates were selected if the reduction of OFV of 3.84 (χ^2 distribution, P =0.05, degree of freedom=1) or more from base model was archived. During backward elimination, covariates at the P≤0.01 (in case of difference of OFV with 6.64 or more increase compared with previous model) were retained in the model.

Model evaluation and validation

The reliability and stability of the population pharmacokinetic model were tested by a nonparametric bootstrap procedure and VPC. During bootstrap procedure (n=1,000), data were randomly resampled to form a new data set from original ones. One thousand replicated data sets were simulated from each of the above-developed models. The observed data were covered with the 5th, 50th, and 95th percentiles of the simulated data calculated at each time point.

Results

One hundred and forty-five patients were included in this analysis and one thousand and nine hundreds thirty-eight blood samples were analyzed. The characteristics of included GN patients are summarized in Table 1 and 2. Patients were predominantly female (63.5%) and immunoglobulin A nephropathy was the most common diagnosis among included patients. The majority of patients seemed to have normal to moderately impaired renal function (estimated glomerular filtration rate: 76.58 ± 30.57 ml/min). Many patients also showed mild proteinuria and mild hypoalbuminemia. The average urine protein to creatinine ratio was 1.83 ± 3.0, and the mean serum albumin level was 3.82 ± 0.59 mg/dL. Concomitantly used medications that possibly have a pharmacokinetic drug interaction with tacrolimus were rosuvastatin(ROSU), steroids (STER), omeprazole (OMEP), nifedipine (NIFE), and rifampin (RIFA).

Although two compartments model with lag time was known to give the best fit for tacrolimus, two compartments model and absorption lag time model were tested and gave worse fit compared to one compartment model in this study. Hence, one compartment model with linear absorption and first-order elimination were selected and exponential error model best described the interindividual as well as residual variability. Among the tested covariates, PCR, WBC, HEMO, PLT, BUN, SCR, CHOL, TPRO, ALB, URIC, TBIL, ALT, BWT, and AGE were selected as covariates for the CL/F in the full model (ΔOFV >3.84; P< 0.05). Since hemoglobin (HEMO) highly correlated with hematocrit (HCT) as with AST and ALT, only the ones showed the larger decrease in OFV were selected. The inclusion of HCT, PLT, BUN, SCR, CHOL, TPRO, ALB, URIC, TBIL, AGE, OMAC, Steroid, OMEP, NIFE, RIFA, Dz in the covariate model for the V/F significantly improved the model (ΔOFV >3.84; P< 0.05). Again, hematocrit (HCT) was highly correlated with hemoglobin (HEMO) and thus, HCT was selected since it showed the larger ΔOFV.

Etiology of glomerulonephritis	n (%)	Concomitantly used medications that may change tacrolimus serum level	n (%)
Minimal change disease (MCD)	32 (22.1)	Rosuvastatin (ROSU)	36 (24.8)
Membranous nephropathy (MN)	11 (7.6)	Steroids (STER)	47 (32.4)
Focal segmental glomerulosclerosis (FSGS)	12 (8.3)	Omeprazole (OMEP)	4 (2.7)
IgA nephropathy	40 (27.6)	Nifedipine (NIFE)	3 (2.0)
Membrano-proliferative glomerulonephritis (MPGN)	6 (4.1)	Rifampin (RIFA)	1 (0.6)
Lupus nephritis	19 (13.1)		
Glomerulonephritis (GN)	5 (3.4)		
Henoch-Schönlein purpura nephritis (HSP)	5 (3.4)		
Other glomerulonephritis	15 (10.3)		

Table 2: Etiology of glomerulonephritis and concomitantly used medications that cause pharmacokinetic drug interaction in included patients.

During the backward elimination process to get the final model, all the covariates except serum creatinine in CL/F and V/F, and serum albumin in V/F were removed (ΔOFV> 7.88; P<0.005). The final model was as follows;

$$\text{Typical Value}\frac{\text{CL}}{\text{F}}\left(\frac{\text{L}}{\text{hr}}\right) = {}_1 \times e^{\theta_5 \times (\text{SCR}-1.12)}$$

$$\text{Typical Value}\frac{\text{V}}{\text{F}}(L) = {}_2 \times e^{\theta_4 \times (\text{SCR}-1.12)} \times e^{\theta_6 \times (\text{ALB}-3.82)}$$

	Male Gender, %	Age	Duration of Tx, days	BWT, kg	Conc, ng/mL	Urine PCr	WBC, K/μL	HEMO, g/dL	HCT, %	PLT, K/μL
Range	36.5	19 - 76	14-886	39 - 157	0-32.6	0.02 - 61.06	1.49 - 24.72	6.4 - 19.2	22.2-55	5 - 585
Mean		39.2	619.5	64	1.54	1.83	9.28	13.44	40.34	246.8
SD		13.7	518	15.7	2.95	3.0	3.38	1.75	4.7	67.7
	BUN, mg/dL	SCR, mg/dL	GFR, ml/min	CHOL, mg/dL	TPRO, mg/dL	ALB, mg/dL	Uric acid g/dL	TBIL, mg/dL	AST, IU/L	ALT, IU/L
Range	4 - 496	0.39 - 13.85	5-193	95 - 894	3.1 - 8.9	1.2 - 5.5	1.8 - 17.3	0.2 - 3.5	7-442	1 - 686
Mean	20.6	1.12	76.58	195.7	6.32	3.82	6.45	0.73	20.9	25.25
SD	16.7	0.8	30.57	67	0.83	0.59	1.8	0.33	14	26

Table 1. Baseline characteristics of patients (n=145).
Tx, Treatment; BWT, body weight; Conc, concentration; PCR, protein creatinine ration; WBC, white blood cell; HEMO, hemoglobin; HCT, hematocrit; PLT, platelet, BUN, blood urea nitrogen; SCR , serum creatinine level; GFR, estimated glomerular filtration rate; TPRO, total protein; ALB, serum albumin; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase

The predicted population parameter estimates obtained from the bootstrap procedure were highly correlated with the estimation of the final model. The estimated mean values were all within VPC estimates of 2.5th and 97.5th percentile range (Table 3).

Pharmacokinetic parameter		Final data estimate			Bootstrap		
Pharmacokinetic parameter	Symbol (code)	Population mean	Standard error	Interindividual variability (%)	Median	2.5th percentile	97.5th percentile
K_a	θ_1	4.5					
CL/F	θ_2	19.5	2.15	11	19.352	14.997	23.944
V/F	θ_3	380	72.7	19	385.093	237.517	522.484
SCR on V/F	θ_4	- 0.22	0.06	27	-0.2167	-0.3352	-0.1014
SCR on CL/F	θ_5	- 0.341	0.141	41	-0.3489	-0.6258	-0.0569
ALB on V/F	θ_6	0.0821	0.028	34	0.04845	0.0271	0.13692
Residual proportional variance (σ)		0.266					

Table 3: Final population pharmacokinetic parameters of tacrolimus and bootstrap validation.

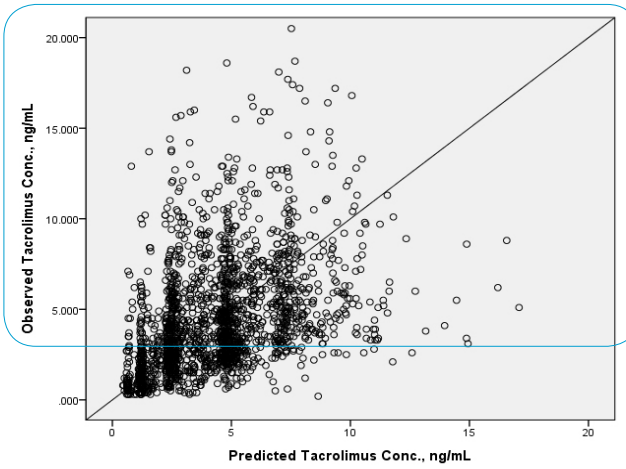

Figure 1: Demonstration of goodness of fit (a) predicted concentration versus observed concentration; (b) conditional weighted residuals versus predicted concentration.

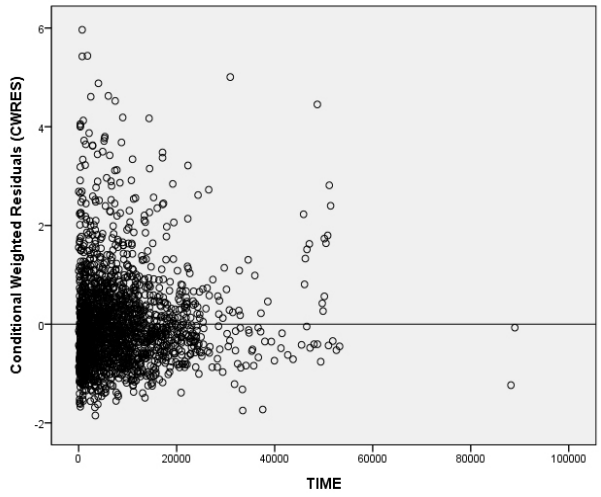

Figure 2: Scatter plot of pharmacokinetic parameters versus selected covariates in final model (a) apparent clearance versus serum creatinine level (SCR); (b)apparent volume of distribution(Vd/F) versus serum creatinine level (SCR); (c) volume of distribution (Vd/F) versus serum albumin level (ALBU).

Discussion

Although population pharmacokinetic studies were frequently performed in transplantation patients, this is the first study examined population pharmacokinetics of tacrolimus in GN patients and explored various factors including concomitantly used medications[24, 25]. Other immunosuppressants such as cyclosporine and mycophenolic acid were studied in GN patients, but there is no information on tacrolimus pharmacokinetics in GN in the literature so far[19]. Understanding population pharmacokinetics of tacrolimus is critical in GN patients in that high serum level may decrease renal function even more in GN patients who are vulnerable to renal toxins. The Ministry of Food and Drug Safety (MFDS) in South Korea recommends checking the serum tacrolimus level regularly to avoid drug toxicity in lupus nephritis patients[7].In practice, poor correlation between dose and concentration was frequently observed due to pharmacokinetic characteristics of the drug. Because trial and error approach was commonly utilized in the management of GN patients on tacrolimus, the pharmacokinetic prediction would be helpful in deciding the tacrolimus dose and guiding the treatment regimen to treat GN. Hence, this study is designed to predict pharmacokinetics of tacrolimus in GN patients.

In this study, the estimated CL/F of 19.5 L/h was found (Figure 1 and Figure 2) to be in good correspondence with the previous reported value of 22.9 L/h although the V/F of 380 L was lower than the previously reported one[24, 26-32]. This is explained by that a lot of previous studies were done in liver transplantation patients possibly with impaired hepatic function. Referenced by Prograf® package insert, theVd of tacrolimus was 0.85 L/kg in healthy volunteer, 1.07 L/Kg in renal impairment, and 3.1-3.9L/kg in patients with hepatic disease[33]. Therefore V/F of 380L, given Vd of 1.1875 L/Kg and bioavailability (F) of 0.2 in a person weighing 64 kg, seemed to be a reasonable estimate considering the renal and hepatic function of study subjects.

The final model reveals that serum creatinine level in CL/F and V/F, as well as serum albumin level in V/F, improved model prediction. Reduced renal function decreased the clearance of tacrolimus although tacrolimus is mainly excreted through hepatic pathway. In practice, patients with decreasing kidney function needs to have reduced tacrolimus doses and should be frequently monitored for serum tacrolimus level. Apparent tacrolimus volume of distribution was also reduced as deteriorating renal function. On the other hand, elevated serum albumin level causes plasma volume expansion and thus, increases the volume of distribution of tacrolimus in GN

patients. Patients with hypoalbuminemia due to heavy proteinuria may require reduced tacrolimus dose and frequent monitoring of serum level. Many covariates were not selected in the final model. Protein creatinine ratio in urine was expected to be selected as covariates but the effect may be too small to show any significance in tacrolimus pharmacokinetics. Concomitantly used medications were also not selected in the final model. The effect of drug interaction might have been smaller than the one of random errors. Another possible explanation is that there were not many patients who were on medications that cause drug interaction. It led to reduced power to detect the difference.

There are a couple of limitations in this study. First, trough blood tacrolimus concentration was used in our analysis mainly due to data availability. Rich concentration data might precisely estimate pharmacokinetics of tacrolimus in GN. Second, although pharmacogenomicfactors are known to be strongly associated with pharmacokinetic variation of tacrolimus, it could not be tested in this study due to unavailability of data[24]. Consideration of genetic factors might have been improved the study result. Third, due to the retrospective study design, patients could not be controlled, and that leads to huge variation in serum tacrolimus levels. For instance, some patients took their blood level checked right after taking medications which was coincidentally found while reviewing patient's records. Poor compliance in GN patients compared to well-educated transplanted patients was also observed. Transplant patients were provided with man to man medication counseling sessions by pharmacists at the practice site while GN patients were not. Additionally, many GN patients seemed to show poor understating of why they are taking immunosuppressant medications and why it is important to take medications correctly. Further study with prospective controlled design considering pharmacogenomics variables would give more predictive pharmacokinetic explanation in GN patients.

Conclusion

Understanding tacrolimus pharmacokinetics and various pharmacokinetic factors are clinically important in GN. The findings of this study indicate that increased serum creatinine level is associated with reduced clearance and reduced volume of distribution of tacrolimus. It also demonstrates that the apparent volume of tacrolimus increases as serum albumin level rises. Developed tacrolimus pharmacokinetic model would offer evidence-based guidance for tacrolimus dosing in GN patients and eventually improve patients' therapeutic outcome.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

MKS, NH and J-MO: Participated in research design.
MKS, JK, KC, NH and EJ: Participated in writing of the paper.
MKS, and MK: Performed data analysis.
J-MO: Made final revisions.

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