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ORIGINAL ARTICLE

Analysis of time course and dose effect of tacrolimus on proteinuria in lupus nephritis patients

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Abstract

What is known and objectives: Tacrolimus is used to treat patients with lupus nephritis; however, its time course and dose effect on proteinuria in lupus nephritis patients remain unknown. The purpose of this study was to determine the time course and dose effect of tacrolimus on proteinuria in lupus nephritis patients via model-based meta-analysis (MBMA).

Methods: PubMed, Web of Science, Cochrane Library and ClinicalTrials.gov databases were systematically searched for information on the efficacy of tacrolimus against proteinuria in lupus nephritis patients. Useful data were extracted to build a model for the population studied using a non-linear mixed-effect model (NONMEM). This model was applied to simulate time course of tacrolimus on proteinuria using Monte Carlo simulations.

Results: Ten clinical studies that recruited 222 patients with lupus nephritis were included. Based on various diagnostic plots, we found that the established model described the observed data reasonably well. In addition, the typical E_{max} and ET_{50} of tacrolimus for 24-hour proteinuria in lupus nephritis patients were −5.88 g and 0.37 months, respectively. The baseline value of 24-hour proteinuria affected E_{max}. No significant dose-response relationship was observed in the range of tacrolimus concentration used in the present study (3-10 ng/mL), indicating that the effect of tacrolimus on proteinuria depends on effective concentration range and not the dose. However, the time course relationship was obvious; the efficacy of tacrolimus increased over time, reaching a plateau (80% E_{max}) at approximately 1.48 months from the beginning of treatment.

What is new and conclusion: When the concentration range of tacrolimus is maintained at 3-10 ng/mL, at least 1.48 months of treatment is required to achieve a better outcome with regard to proteinuria in lupus nephritis patients.

KEYWORDS

dose effect, lupus nephritis, model-based meta-analysis, proteinuria, tacrolimus, time course

Xiao Chen and Dong-Dong Wang contributed equally to this study.

1 | WHAT IS KNOWN AND OBJECTIVES

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs.[1] Complex interaction between the genetic environment and hormones leads to immune dysregulation and a subsequent breakdown in tolerance to autoantigens, resulting in inflammation of autoantibodies and destruction of organs.[2] Different organs are involved in various manifestations, at the same time or successively, including the urinary, nerve, cardiovascular, blood and other systems.[3-6] Among these, lupus nephritis is one of the most severe complications of SLE and its incidence rate is up to 60% of patients with SLE.[7] If not treated with proper medication, lupus nephritis can lead to irreversible kidney damage and subsequently deteriorate into end-stage renal disease.

As is known to all, proteinuria is an important risk indicator for progression of kidney damage in lupus nephritis patients. Hence, controlling proteinuria is particularly important for the treatment of lupus nephritis.[8] Many studies have found that tacrolimus has been used to treat patients with lupus nephritis and has had a good effect on controlling proteinuria.[9-11] In addition, a published systematic review and meta-analysis also confirmed that tacrolimus may be more effective at reducing proteinuria, having potential implications for long-term outcome.[12] However, the time course and dose effect of tacrolimus on proteinuria in patients with lupus nephritis remain unknown. This is because the meta-analysis methodology has its own limitations. For example, meta-analysis usually ignores the inter-trial heterogeneity of the included studies. In addition, traditional meta-analysis usually analysed only the endpoint efficacy; the entire time-effect process could not be described.[13] In other word, it is unknown how long it takes for tacrolimus treatment on proteinuria in lupus nephritis patients. Therefore, a new method is needed to assess the time course and dose effect of tacrolimus on proteinuria in lupus nephritis patients.

Model-based meta-analysis (MBMA) is a key tool for model-informed drug discovery and development,[14] which enables accurate description of the time course and dose-effect relationships from drugs.[15,16] Compared to the traditional meta-analysis, the efficacy data of each time point can be fully utilized by MBMA.[15,16] Therefore, the purpose of this study was to explore the time course and dose effect of tacrolimus on proteinuria in lupus nephritis patients using MBMA.

2 | METHODS

2.1 | Search strategy

A comprehensive literature search was conducted using PubMed, Web of Science, Cochrane Library and ClinicalTrials.gov databases up to December 2019, with the terms 'lupus nephritis' and' tacrolimus'. Inclusion criteria were as follows: (I) clinical studies; (II) studies including tacrolimus dosing; (III) reports with details on tacrolimus dosing regimen and drug contact time; and (IV) studies with information about changes in proteinuria. Patient treatment information and data on 24-hour proteinuria were extracted from published studies qualifying all the inclusion criteria.

2.2 | Data extraction and model development

Data were extracted from the published studies, including country, number of patients, treatment duration, tacrolimus dose, sex, age, drug combination, baseline value of 24-hour proteinuria and the change in 24-hour proteinuria from baseline.

Owing to the change in 24-hour proteinuria, proteinuria varied with time and reached a plateau, which was in-line with the E_{max} model. Thus, the E_{max} model was used to assess the effect of tacrolimus on proteinuria in lupus nephritis patients in the present study as shown in Equation (1):

$$E_{i,j} = \frac{(E_{max} \times \exp(\eta_{1,i})) \times \text{Time}_j}{(ET_{50} \times \exp(\eta_{2,i})) + \text{Time}_j} + \frac{\varepsilon_{i,j}}{\sqrt{\frac{N_{i,j}}{100}}}. \quad (1)$$

$E_{i,j}$ represents the change in 24-hour proteinuria from baseline at the observation time point j in the study i. E_{max} is the theoretical maximum change of 24-hour proteinuria from baseline. ET_{50} represents the treatment duration to reach half of the maximal change in 24-hour proteinuria from baseline. $\eta_{1,i}$ and $\eta_{2,i}$ are the inter-study variabilities of E_{max} and ET_{50}, assumed to be normally distributed with a mean of 0 and variance of ω_1^2 and ω_2^2, respectively. $\varepsilon_{i,j}$ represents the residual error of study i with j time, and $N_{i,j}$ is the sample size in study i with time point j. $\varepsilon_{i,j}$ is weighted by sample size, assumed to be normally distributed, with a mean of 0 and variance of $\sigma^2/(N_{i,j}/100)$.

When the covariate model was built, categorical covariates were evaluated according to Equation 2, whereas the continuous covariates were evaluated using Equation 3 or Equation 4:

$$P_{popur} = P_{Typle} + \text{COV}\theta_{covar}, \quad (2)$$

$$P_{popur} = P_{Typle} + (\text{COVA} - \text{COVA}_{media}) \cdot \theta_{covar}, \quad (3)$$

$$P_{popur} = P_{Typle} (\text{COVA}/\text{COVA}_{media}), \theta_{covar}. \quad (4)$$

P_{popur} is the model parameter for a patient with a covariate value of COVA. $COVA_{media}$ is the median value of the covariable in the population. P_{Typle} is the typical value of the parameter when categorical covariates are equal to 0 or continuous covariates are equal to $COVA_{media}$. θ_{covar} is the correction coefficient of the covariate to the model parameter.

NONMEM was used for model development. Once the basic model is completed, potential covariates such as country, treatment duration, tacrolimus dose, sex, age, drug combination and baseline value of 24-hour proteinuria are considered to add into E_{max}. The covariate model was established using the forward inclusion-backward

elimination method.[17] During the forward addition, covariates at the $P < .05$ level were included in the model, and during backward elimination, covariates at the $P < .01$ level were retained in the model.[17]

2.3 | Model validation

The accuracy of the final model fit was assessed by visual inspection of routine diagnostic plots. Monte Carlo simulations were performed 1000 times to predict 95% confidence intervals of the parameters from the final model. Prediction-corrected visual predictive check plots were used for assessing final model predictive performance.

2.4 | Prediction

The curve of efficacy compared with E_{max} from the final model was simulated by Monte Carlo method, and the time required to achieve 50%, 60%, 70%, 80%, 90%, and 95% E_{max} of tacrolimus on proteinuria in lupus nephritis patients.

2.5 | Software

The model estimation and simulation were performed using NONMEM software (edition 7, ICON Development Solutions).

3 | RESULTS

3.1 | Included patients

An overview of the strategy for literature review is shown in Figure 1, which identified ten clinical studies and a total of 222 patients with lupus nephritis. As shown in Table 1, the sample size ranged from 7 to 74; the treatment duration ranged from 6 to 36 months; tacrolimus

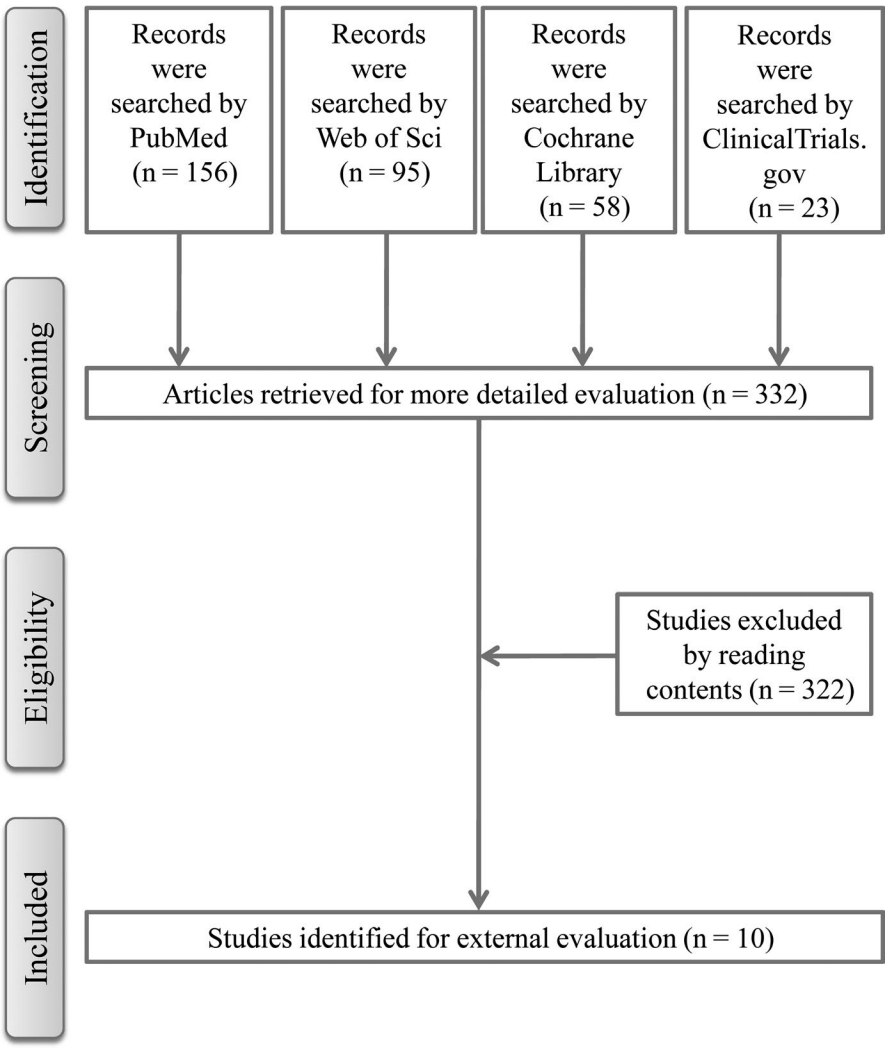

FIGURE 1 Overview of the strategy for literature review

TABLE 1 Characteristics of studies included in the model-based meta-analysis data set

Study	Nationality	Patients (n)	Treatment duration (mo)	Tacrolimus dosage	Male (%)	Age (y)	Drug combination
Mok et al 2005	China	9	6	The initial dose was 0.1 mg/kg/day, beginning from the third month, and the dose of tacrolimus was reduced to 0.06 mg/kg/day and maintained until the end of 6 months (flexible)	33.33	33.3	Prednisolone
Mok et al 2016	China	74	6	Tacrolimus initial dosage 0.1 mg/kg/day, reduced to 0.06 mg/kg/day if clinical response was satisfactory at month 3 (flexible)	5.41	36.2	Prednisolone
Lee et al 2010	Korea	9	12	The starting dosage was 0.1 mg/kg/day (flexible)	11.11	31.0	Prednisolone
Mao et al 2019	China	11	36	Tacrolimus 0.05 mg/kg was administered at onset, and the maximum dose was 2 mg (flexible)	27.27	10.5	Prednisolone, ciclosporin
Fei et al 2013	China	26	6	The initial dose was 2 mg/day (body weight < 60 kg) or 3 mg/day (body weight ≥ 60 kg). If patients did not respond after 2 months of treatment, the dosage was increased to a maximum of 4 mg/day and maintained throughout the study period. Change in tacrolimus dose was generally made in steps of 0.5 mg per 2 weeks (flexible)	15.38	29.4	Prednisolone
Kagawa et al 2012	Japan	8	6	The initial dosage was 3 mg/day (flexible)	0	48.5	Prednisolone, mizoribine
Bao et al 2008	China	20	9	The dosage of tacrolimus was initiated at 4 mg/day (3 mg/day for patients weighing ≤50 kg; flexible)	20.00	27.2	Prednisolone, Mycophenolate mofetil
Wang et al 2019	China	7	12	2-3 mg/day (flexible)	42.86	14.2	Prednisolone
Szeto et al 2008	China	18	6	Tacrolimus was started at daily dose of 0.1-0.2 mg/kg/day (flexible)	11.11	38.2	Prednisolone
Wang et al 2012	China	40	12	The initial dosage was 0.08 mg/kg/day for patients with eGFR more than 40 mL/min/1.73 m^2 and 0.04 mg/kg/day for patients with eGFR <40 mL/min/1.73 m^2 (flexible)	20.00	33.9	Prednisolone

dosage was flexible, and the range of tacrolimus concentration used in the present study was 3-10 ng/mL.

3.2 | Model and evaluation

The parameter values of the final model are shown in Table 2. The typical E_{max} and ET_{50} of tacrolimus on 24-hour proteinuria in lupus nephritis patients were −5.88 g, and 0.37 months, respectively. The baseline value of 24-hour proteinuria had an impact on E_{max}, which can be quantified as follows:

For every 1g increased in the baseline value of 24-hour proteinuria, the E_{max} increased by 0.98 g. No significant dose-response relationship was observed in the range of tacrolimus concentration in the present study (3-10 ng/ml), thus showing that the effect of tacrolimus on proteinuria in lupus nephritis patients depends on the effective tacrolimus concentration range, not the dose.

$$E_{max} = -5.88 + (\text{baseline} - 4.41)(-0.98). \quad (5)$$

In addition, as shown in Table 2, 95% confidence intervals for the parameters of the final model from Monte Carlo simulations indicated the stability of the model well. Individual predictions *vs*. observations, population predictions *vs*. conditional weighted residuals (WRES) and conditional WRES *vs*. time are shown in Figure 2, showing the good fitting of the final model. The visual predictive check plots were used to assess the predictive performance of the final model, as shown in Figure 3, and most observed data were included in the 95% prediction intervals produced by

TABLE 2 Parameter estimates of final model and 95% confidential interval

Parameter	Estimate	SE (%)	Simulation (n = 1000)	
			Median	95% confidence interval
E_{max}, g	−5.88	67.9	−5.88	[−5.88, −5.88]
ET_{50}, month	0.37	15.7	0.37	[0.37, 0.75]
$\theta_{Baseline}$	−0.98	–	−0.98	[−0.98, −0.98]
$\omega_{E_{max}}$	0.488	1.3	0.489	[0.003, 0.597]
$\omega_{ET_{50}}$	1.200	13.4	1.158	[0.003, 2.178]
ε	0.404	18.7	0.409	[0.249, 1.123]

Note: 95% confidential interval was displayed as the 2.5th and 97.5th percentiles of Monte Carlo simulations. E_{max}, E_{max} of tacrolimus on 24-h urine protein in lupus nephritis; ET_{50}, ET_{50} of tacrolimus on 24-h urine protein in lupus nephritis; $\theta_{Baseline}$, impact of baseline of 24-h urine protein in lupus nephritis on E_{max}; $\omega_{E_{max}}$, inter-study variability of E_{max}; $\omega_{ET_{50}}$, inter-study variability of ET_{50}; and ε, residual error.

simulation data, which demonstrated the predictive power of the final models.

3.3 | Prediction

The curve of efficacy compared with E_{max} with time is shown in Figure 4. The efficacy of tacrolimus at 0.37 months was only about 50% of the E_{max} drug value, and the ratio increased to 60% at 0.56 months, 70% at 0.87 months, 80% at 1.48 months, 90% at 3.33 months and 95% at 7.03 months. That is to say, at least 1.48 months of treatment is required to achieve a plateau (80% E_{max}).

4 | DISCUSSION

Tacrolimus is a first-line immunosuppressant that has been widely used for liver,[18] kidney,[19] haematopoietic stem cell transplantations,[20]

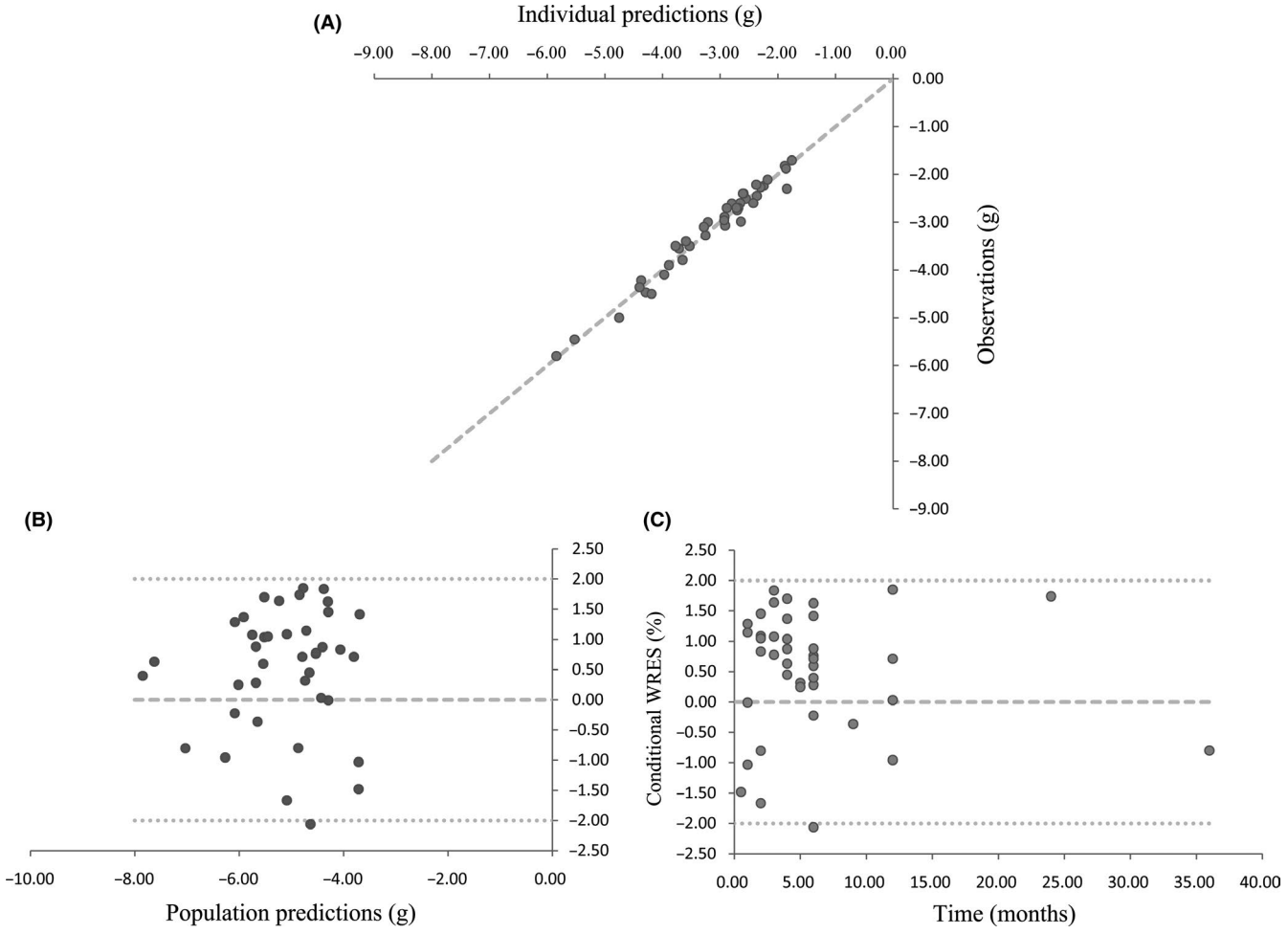

FIGURE 2 Visual inspection of routine diagnostic plots. A, Individual predictions vs. observations, B, population predictions *vs.* conditional weighted residuals (WRES) and C, conditional WRES *vs.* time

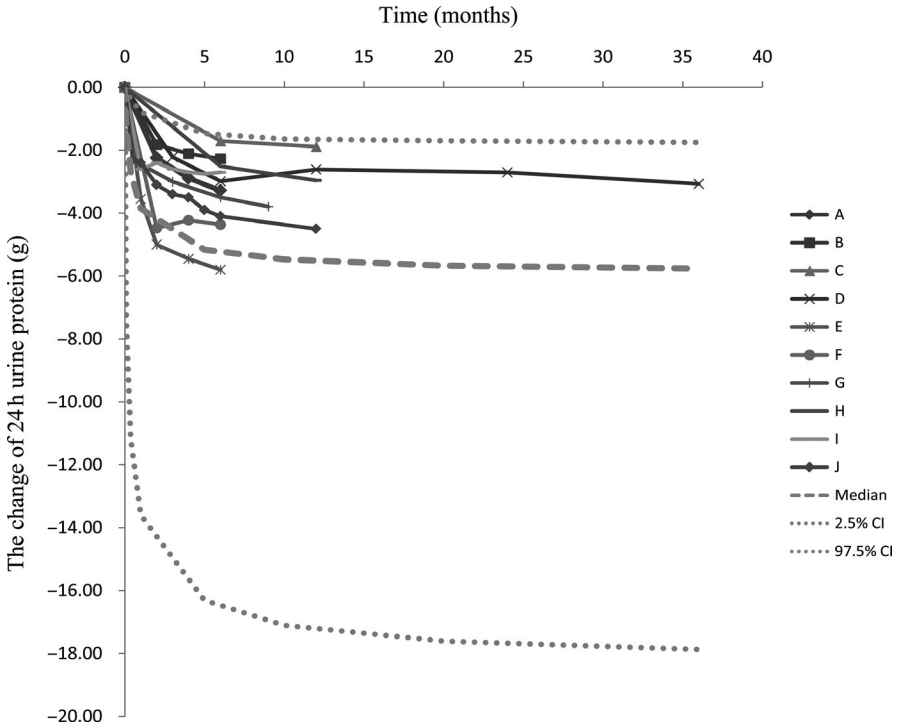

FIGURE 3 Prediction-corrected visual predictive check plots. A: Mok et al 2005[23]; B: Mok et al 2016[24]; C: Lee et al 2010[25]; D: Mao et al 2019[26]; E: Fei et al 2013[27]; F: Kagawa et al 2012[28]; G: Bao et al 2008[29]; H: Wang et al 2019[30]; I: Szeto et al 2008[31]; J: Wang et al 2012[32]; Median, 2.5% CI and 97.5% CI were simulated by Monte Carlo (n = 1000); CI, confidence interval

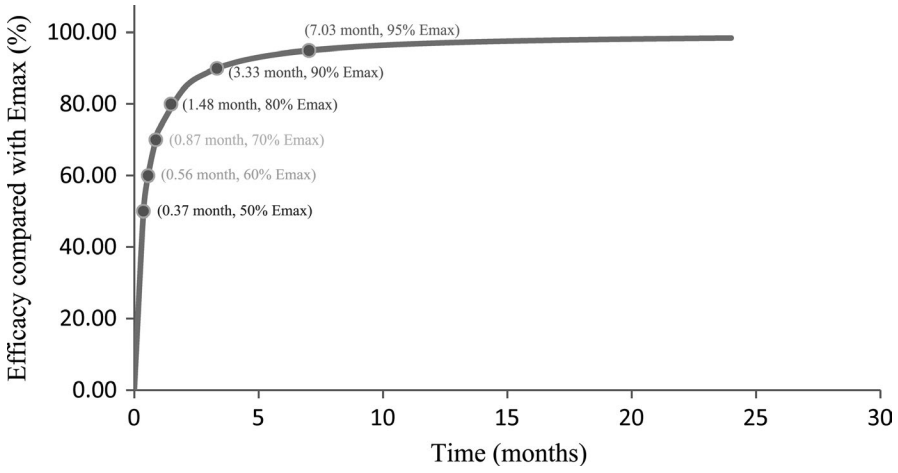

FIGURE 4 Model prediction. E_{max}, the theoretical maximum change of 24-hour proteinuria from baseline

systemic lupus erythematosus,[21] lupus nephritis[22] and other diseases. The use of tacrolimus for the treatment of lupus nephritis, especially proteinuria, can be significantly reduced.[23-32] The purpose of this study was to quantify the effect of tacrolimus on proteinuria and provide valuable information regarding proteinuria treatment in patients with lupus nephritis using MBMA.

In recent years, MBMA, a new quantitative analysis method, has been used in pharmaceutical research.[15,33-44] The general steps of MBMA include (a) collecting clinical study data from relevant literature; (b) combining clinical studies and establishing a pharmacodynamic model and statistical model; (c) introducing potential covariates to investigate the effect of drug dose, course of treatment, baseline and other factors on efficacy, and establishing a final model; and (d) predicting the efficacy of different drug regimens or time required to achieve the desired efficacy based on the simulation of the final model. For example, Luu et al reported a model-based meta-analysis of the effect of latanoprost chronotherapy on the circadian intraocular pressure in patients with glaucoma or ocular hypertension.[45] Li et al reported the quantitative efficacy of soy isoflavones on menopausal hot flashes[46]; Renard et al reported characterization of the bronchodilatory dose response to indacaterol in patients with chronic obstructive pulmonary disease using model-based approaches.[47] In summary, MBMA has become an important tool for comparing drug efficacy, making drug development decisions, and optimizing clinical delivery protocols for drug development.

To our knowledge, this is the first study to explore the quantitative efficacy of tacrolimus on proteinuria in lupus nephritis patients. A total of 222 patients with lupus nephritis were included from China, Japan and Korea. In the final model, the typical E_{max} and ET_{50} of tacrolimus on 24-hour proteinuria in lupus nephritis patients were −5.88 g and 0.37 months, respectively. The baseline value of 24-hour proteinuria had an impact on E_{max}. For every 1 g increase in the baseline value of

24-hour proteinuria, the E_{max} increased by 0.98 g. In addition, no significant dose-response relationship was observed in the range of tacrolimus concentration involved in the present study (3-10 ng/mL), showing that the effect of tacrolimus on proteinuria depended on its effective concentration range, not the dose. The result was explicable; tacrolimus was transported by P-glycoprotein,[48] which is an energy-dependent transmembrane efflux pump (adenosine triphosphate–binding cassette B1) encoded by the multidrug resistance 1 (*ABCB1*) gene.[49] In addition, it was metabolized via hepatic cytochrome P450 (*CYP*)3A4 and *CYP3A5* in the liver and intestine, and subsequently eliminated into the bile.[50] Patients carrying uncertain gene polymorphisms can profoundly influence the relationship between dose and tacrolimus concentration. In other words, its concentration may also vary significantly between patients with different genotypes at the same dose. Since there is no significant dose-response relationship, clinical efficacy is rarely measured by tacrolimus dose; instead, the drug concentration is controlled within a certain range. Many studies have reported that the clinical use of tacrolimus in transplantation,[51] nephrotic syndrome[52] and SLE[21] was also based on maintaining the concentration within a certain range using therapeutic drug monitoring. In fact, many drugs in combination can affect the metabolism of tacrolimus, and the advantage of using the tacrolimus window in this study is that we can adjust its flexible dose to keep the concentration within the window through routine therapeutic drug monitoring, simplifying the complex clinical problems. In other words, regardless of how other treatments affect tacrolimus concentration, there is need to flexibly increase or decrease the dose of tacrolimus to get to the required treatment window. The same is true for its usage in patients with kidney transplants; due to the inter- and intra-individual differences in pharmacokinetics of tacrolimus during treatment, its clinical dose is often flexible rather than fixed, and the relationship between tacrolimus and its efficacy is often measured by drug concentration rather than dose. For example, the target concentration of tacrolimus in patients with kidney transplants within the therapeutic window of 5-15 ng/mL is considered effective,[51,53] instead of a fixed dose.

Additionally, based on the clinical trials identified so far, particularly the ten clinical studies including a total of 222 patients with lupus nephritis, the range of tacrolimus concentration used in the present study was 3-10 ng/mL, in which the tacrolimus concentration is effective for the treatment of urinary protein in lupus nephritis. In addition, while maintaining the tacrolimus concentration range at 3-10 ng/mL, the duration to achieve 50%, 60%, 70%, 80%, 90% and 95% of efficacy against proteinuria in lupus nephritis patients was 0.37, 0.56, 0.87, 1.48, 3.33 and 7.03 months, respectively. This indicates that at least 1.48 months of treatment is required to achieve a plateau (80% E_{max}).

5 | WHAT IS NEW AND CONCLUSION

This is the first study to explore the quantitative efficacy of tacrolimus on proteinuria in lupus nephritis patients; it provides valuable quantitative information regarding the efficacy of tacrolimus against proteinuria in the population studied. With a tacrolimus concentration range of 3-10 ng/mL, a treatment duration of 1.48 months is required to achieve better outcome with regard to proteinuria in lupus nephritis patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Dorner T, Furie R. Novel paradigms in systemic lupus erythematosus. *The Lancet*. 2019;393:2344-2358.
2. Moulton VR, Suarez-Fueyo A, Meidan E, Li H, Mizui M, Tsokos GC. Pathogenesis of human systemic lupus erythematosus: a cellular perspective. *Trends Mol Med*. 2017;23:615-635.
3. Huang C, Yi X, Long H, et al. Disordered cutaneous microbiota in systemic lupus erythematosus. *J Autoimmun*. 2019; 108:102391.
4. Kandane-Rathnayake R, Kent JR, Louthrenoo W, et al. Longitudinal associations of active renal disease with irreversible organ damage accrual in systemic lupus erythematosus. *Lupus*. 2019;28:1669-1677.
5. Akaho R, Nishimura K. Neuropsychiatric systemic lupus erythematosus: psychiatric symptoms. *Brain Nerve*. 2019;71:473-481.
6. Kostopoulou M, Nikolopoulos D, Parodis I, Bertsias G. Cardiovascular disease in systemic lupus erythematosus: recent data on epidemiology, risk factors and prevention. *Curr Vasc Pharmacol*. 2019;18. https://doi.org/10.2174/1570161118666191227122710163. Epub ahead of print.
7. Mok CC, Tang SS. Incidence and predictors of renal disease in Chinese patients with systemic lupus erythematosus. *Am J Med*. 2004;117:791-795.
8. Hara R, Miyazawa H, Nishimura K, et al. A national survey on current use of mycophenolate mofetil for childhood-onset systemic lupus erythematosus in Japan. *Mod Rheumatol*. 2015;25:858-864.
9. Wang DD, Chen X, Li ZP. Efficacy and safety of tacrolimus in Chinese lupus nephritis patients: a meta-analysis. *Int J Clin Exp Med*. 2019;12:3056-3064.
10. Gordon S, Denunzio T, Uy A. Success using tacrolimus in patients with proliferative and membranous lupus nephritis and refractory proteinuria. *Hawai'i J Med Public Health*. 2013;72:18-23.
11. Almutairi A, Alkathiri Z, Al-Mayouf SM. Combination of tacrolimus and mycophenolate mofetil in persistent proteinuria due to refractory childhood lupus nephritis. *Int J Pediatrics Adolesc Med*. 2018;5:99-102.
12. Hannah J, Casian A, D'Cruz D. Tacrolimus use in lupus nephritis: A systematic review and meta-analysis. *Autoimmun Rev*. 2016;15:93-101.
13. Cheung MW, Vijayakumar R. A guide to conducting a meta-analysis. *Neuropsychol Rev*. 2016;26:121-128.
14. Lalonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development. *Clin Pharmacol Ther*. 2007;82:21-32.
15. Boucher M, Bennetts M. The many flavors of model-based meta-analysis: part I-introduction and landmark data. *CPT: Pharmacometrics Syst Pharmacol*. 2016;5:54-64.
16. Cheng Q, Huang J, Xu L, et al. Analysis of time-course, dose-effect, and influencing factors of antidepressants in the treatment of acute adult patients with major depression. *Int J Neuropsychopharmacol*. 2020;23:76-87.
17. Zheng X, He Y, Xu L, et al. Quantitative analysis of the placebo response in pharmacotherapy of insomnia and its application in clinical trials. *Sleep*. 2020;43.

18. Wang DD, Chen X, Fu M, Zheng QS, Xu H, Li ZP. Model extrapolation to a real-world dataset: evaluation of tacrolimus population pharmacokinetics and drug interaction in pediatric liver transplantation patients. *Xenobiotica*. 2020;50:371-379.
19. Allegri L, Baldan F, Vallone C, et al. Tacrolimus therapeutic drug monitoring in stable kidney transplantation and individuation of CYP3A5 genotype. *Transpl Proc*. 2019;51:2917-2920.
20. Gao Y, Ma J. Tacrolimus in adult hematopoietic stem cell transplantation. *Exp Opin Drug Metab Toxicol*. 2019;15:803-811.
21. Chen X, Wang D, Xu H, Li Z. Initial dose optimization of tacrolimus for children with systemic lupus erythematosus based on the CYP3A5 polymorphism and coadministration with Wuzhi capsule. *J Clin Pharm Ther*. 2019;45:309-317.
22. Zhou T, Lin S, Yang S, Lin W. Efficacy and safety of tacrolimus in induction therapy of patients with lupus nephritis. *Drug Des Dev Therapy*. 2019;13:857-869.
23. Mok CC, Tong KH, To CH, Siu YP, Au TC. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study. *Kidney Int*. 2005;68:813-817.
24. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. *Ann Rheum Dis*. 2016;75:30-36.
25. Lee T, Oh KH, Joo KW, et al. Tacrolimus is an alternative therapeutic option for the treatment of refractory lupus nephritis. *Lupus*. 2010;19:974-980.
26. Mao Y, Yin L, Huang H, Zhou Z, Chen T, Zhou W. Addition of cyclosporine/tacrolimus for pediatric relapsed lupus nephritis during mycophenolate mofetil maintenance therapy. *J Int Med Res*. 2019;47:105-113.
27. Fei Y, Wu Q, Zhang W, et al. Low-dose tacrolimus in treating lupus nephritis refractory to cyclophosphamide: a prospective cohort study. *Clin Exp Rheumatol*. 2013;31:62-68.
28. Kagawa H, Hiromasa T, Hara T, et al. Mizoribine, tacrolimus, and corticosteroid combination therapy successfully induces remission in patients with lupus nephritis. *Clin Exp Nephrol*. 2012;16:760-766.
29. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol*. 2008;19:2001-2010.
30. Wang DD, Chen X, Li ZP. Tacrolimus ameliorates proteinuria in Chinese pediatric lupus nephritis patients. *Int J Clin Exp Med*. 2019;12:10931-10937.
31. Szeto CC, Kwan BC, Lai FM, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology*. 2008;47:1678-1681.
32. Wang S, Li X, Qu L, et al. Tacrolimus versus cyclophosphamide as treatment for diffuse proliferative or membranous lupus nephritis: a non-randomized prospective cohort study. *Lupus*. 2012;21:1025-1035.
33. Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Modelling time-course relationships with multiple treatments: model-based network meta-analysis for continuous summary outcomes. *Res Synth Methods*. 2019;10:267-286.
34. Upreti VV, Venkatakrishnan K. Model-based meta-analysis: optimizing research, development, and utilization of therapeutics using the totality of evidence. *Clin Pharmacol Ther*. 2019;106:981-992.
35. Kashihara Y, Terao Y, Yoda K, et al. Effects of magnesium oxide on pharmacokinetics of L-dopa/carbidopa and assessment of pharmacodynamic changes by a model-based simulation. *Eur J Clin Pharmacol*. 2019;75:351-361.
36. Teng Z, Gupta N, Hua Z, et al. Model-based meta-analysis for multiple myeloma: a quantitative drug-independent framework for efficient decisions in oncology drug development. *Clin Transl Sci*. 2018;11:218-225.
37. Wu J, Xu L, Lv Y, Dong L, Zheng Q, Li L. Quantitative analysis of efficacy and associated factors of calcium intake on bone mineral density in postmenopausal women. *Osteoporos Int*. 2017;28:2003-2010.
38. Mawdsley D, Bennetts M, Dias S, Boucher M, Welton NJ. Model-based network meta-analysis: a framework for evidence synthesis of clinical trial data. *CPT: Pharmacometrics Syst Pharmacol*. 2016;5:393-401.
39. Perez-Pitarch A, Guglieri-Lopez B, Ferriols-Lisart R, Merino-Sanjuan M. A model-based meta-analysis of sofosbuvir-based treatments in chronic hepatitis C patients. *Int J Antimicrob Agents*. 2016;47:184-194.
40. Li HQ, Xu JY, Jin L, Xin JL. Utilization of model-based meta-analysis to delineate the net efficacy of taspoglutide from the response of placebo in clinical trials. *Saudi Pharm J*. 2015;23:241-249.
41. Li HQ, Xu JY, Jin L, Xin JL. The efficacy of placebo-adjusted taspoglutide on body weight reduction in clinical trials. *Pharmazie*. 2015;70:110-116.
42. Dodds MG, Salinger DH, Mandema J, Gibbs JP, Gibbs MA. Clinical trial simulation to inform phase 2: comparison of concentrated vs. distributed first-in-patient study designs in psoriasis. *CPT: Pharmacometrics Syst Pharmacol*. 2013;2(7):e58. https://doi.org/10.1038/psp.2013.32
43. Mould DR. Model-based meta-analysis: an important tool for making quantitative decisions during drug development. *Clin Pharmacol Ther*. 2012;92:283-286.
44. Mandema JW, Gibbs M, Boyd RA, Wada DR, Pfister M. Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond. *Clin Pharmacol Ther*. 2011;90:766-769.
45. Luu KT, Raber SR, Nickens DJ, Vicini P. A model-based meta-analysis of the effect of latanoprost chronotherapy on the circadian intraocular pressure of patients with glaucoma or ocular hypertension. *Clin Pharmacol Ther*. 2010;87:421-425.
46. Li L, Lv Y, Xu L, Zheng Q. Quantitative efficacy of soy isoflavones on menopausal hot flashes. *Br J Clin Pharmacol*. 2015;79:593-604.
47. Renard D, Looby M, Kramer B, Lawrence D, Morris D, Stanski DR. Characterization of the bronchodilatory dose response to indacaterol in patients with chronic obstructive pulmonary disease using model-based approaches. *Respir Res*. 2011;12:54.
48. Moller A, Iwasaki K, Kawamura A, et al. The disposition of 14C-labeled tacrolimus after intravenous and oral administration in healthy human subjects. *Drug Metab Dispo*. 1999;27:633-636.
49. Masuda S, Inui K. An up-date review on individualized dosage adjustment of calcineurin inhibitors in organ transplant patients. *Pharmacol Ther*. 2006;112:184-198.
50. Hebert MF. Contributions of hepatic and intestinal metabolism and P-glycoprotein to cyclosporine and tacrolimus oral drug delivery. *Adv Drug Deliv Rev*. 1997;27:201-214.
51. Zhao W, Elie V, Roussey G, et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther*. 2009;86:609-618.
52. Chen X, Wang DD, Xu H, Li ZP. Optimization of initial dosing scheme of tacrolimus in pediatric refractory nephrotic syndrome patients based on CYP3A5 genotype and coadministration with wuzhi-capsule. *Xenobiotica*. 2020;50:606-613.
53. Chen X, Wang DD, Xu H, Li ZP. Initial dosage optimization of tacrolimus in Chinese pediatric patients undergoing kidney transplantation based on population pharmacokinetics and pharmacogenetics. *Expert Rev Clin Pharmacol*. 2020;13:553-556.

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