Int J Clin Exp Med 2019;12(8):10931-10937
www.ijcem.com /ISSN:1940-5901/IJCEM0095395

*Case Report*

# Tacrolimus ameliorates proteinuria in Chinese pediatric lupus nephritis patients

Dong-Dong Wang[1*], Xiao Chen[2*], Zhi-Ping Li[1]

*[1]Department of Pharmacy, Children's Hospital of Fudan University, Shanghai 201102, China; [2]Department of Pharmacy, The People's Hospital of Jiangyin, Jiangyin 214400, China. [*]Equal contributors.*

Received April 14, 2019; Accepted June 10, 2019; Epub August 15, 2019; Published August 30, 2019

**Abstract:** Few studies have reported treatment with tacrolimus (TAC) for Chinese pediatric lupus nephritis (PLN). Therefore, this study aims to investigate the effects of TAC in Chinese PLN. A 12 month retrospective analysis was performed from Children's Hospital of Fudan University. Data on the clinical characteristics and serologic lupus activity were assembled. The baseline characteristics of the patients were: complement component 3 (C3), 0.64 ± 0.36 g/L; complement component 4 (C4), 0.13 ± 0.09 g/L; the 50% hemolytic complement (CH50), 29.14 ± 21.59 U/ml; erythrocyte sedimentation rate (ESR), 48.43 ± 28.16 mm/h; platelets (PLT), 167.00 ± 87.82 10^9/L; 24 h urine protein, 3.07 ± 1.33 g; prednisolone (PDN) dose, 52.57 ± 7.16 mg/d. After 12 month treatment with TAC, C3, and CH50 levels were increased than baseline ($P < 0.05$). ESR, 24 hour urine protein and PDN dose were decreased than baseline ($P < 0.05$). No serious adverse reactions were found. In conclusion, TAC could ameliorate proteinuria and reduce PDN dose in Chinese PLN patients.

**Keywords:** Tacrolimus, proteinuria, pediatric, lupus nephritis, real world study

## Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production of a large number of autoantibodies in the blood, which deposits in the vascular beds of target tissues and organs including glomeruli and the renal microvasculature, leading to systemic inflammation and lupus nephritis (LN) [1-4].

Pediatric systemic lupus erythematosus (PSLE) is a disease with a prevalence of 4.7 per 100,000 children, where higher frequency of LN is observed in children than adults. It is generally believed that LN lesions could affect prognosis and proteinuria is an important risk factor for progression of renal disease in patients with LN. Therefore, controlling proteinuria is particularly important in treating pediatric lupus nephritis (PLN) [5].

Although corticosteroids and immunosuppressants are widely used to treat PLN, more than a few resistant cases have been experienced. A new treatment has been strongly sought in the clinical setting [6].

Tacrolimus (TAC) is a medication that induces an immunosuppressive effect, and in recent years it has been widely used in the treatment of SLE [7, 8]. However, the experience of TAC in Chinese PLN is very limited. This study aims to investigate the effect of TAC in Chinese PLN.

## Material and methods

### *Patients*

All data were all from real world studies. Patients, younger than 18 years of age, who were diagnosed by LN and on treatment with tacrolimus as therapy, were included in our study. Patients were excluded if they had other serious diseases. PLN patients in Children's Hospital of Fudan University were studied for treatment dates between January 2015 and December 2017, retrospectively. The present study was approved by *the Research Ethics Committee of Children's Hospital of Fudan University.*

*Main outcome variable and procedures*

A systematic review of patient files, using a standard data collection protocol, was carried out. Data were gathered from the beginning of TAC treatment to the 12 month endpoint, defined as last follow-up. Clinical characteristics included sex, age, renal biopsies, TAC dose, complement component 3 (C3), complement component 4 (C4), the 50% hemolytic complement (CH50), erythrocyte sedimentation rate (ESR), platelets (PLT), 24 h urine protein and prednisolone (PDN) dose at the beginning of TAC treatment (0 month), treatment with TAC for 6 months (6 month) and treatment with TAC for 12 months (12 month). Data on clinical characteristics and serologic lupus activity were obtained from medical records, which were measured by the automatic biochemical analyzer.

*Statistical analysis*

Data are expressed as mean ± standard error (SE). Statistical analyses were performed using General Linear Model for repeated measurement. A value of $P < 0.05$ was considered statistically significant.

## Results

*Summary of clinical characteristics*

Clinical characteristics are summarized in **Table 1**. Seven Chinese PLN patients including three boys and four girls from Children's Hospital of Fudan University were available for investigate the effects of TAC in PLN. Their ages were from 9.2 to 17.5. Renal biopsies showed one III, four IV-G, and two V. During follow-up time, TAC dose were 2-3 mg/d. The baseline characteristics of the patients were: C3, 0.64 ± 0.36 g/L; C4, 0.13 ± 0.09 g/L; CH50, 29.14 ± 21.59 U/ml; ESR, 48.43 ± 28.16 mm/h; PLT, 167.00 ± 87.82 10^9/L; 24 h urine protein, 3.07 ± 1.33 g; PDN dose, 52.57 ± 7.16 mg/d.

*Changes in C3, C4 and CH50 after TAC treatment*

As illustrated in **Figure 1**, the C3, C4, and CH50 exhibited remarkably higher level at 6 month when compared to 0 month ($P < 0.05$). This indicated that TAC could significantly improve the low level of C3, C4, and CH50 after treatment with TAC for 6 months in PLN. At 12 month, the level of C3, and CH50 were still higher than 0 month ($P < 0.05$). This showed that TAC could increase C3, and CH50 level after treatment with TAC for 12 months.

*Changes in ESR and PLT after TAC treatment*

In **Figure 2**, ESR after treatment with TAC for 6 months and 12 months were all decreased compared with baseline, 0 month ($P < 0.05$). Thus, the results indicated that administration of TAC significantly decreased the level of ESR in PLN. However, no significant difference was found between baseline and treatment with TAC for 6 or 12 months in terms of the level of PLT.

*Changes in 24 hour urine protein and PDN dose after TAC treatment*

The 24 hour urine protein and PDN dose after treatment with TAC for 6 months and 12 months were all decreased compared with baseline ($P < 0.05$), as shown in **Figure 3**, indicating that TAC could ameliorate 24 hour urine protein and reduce PDN dose in PLN.

## Discussion

PSLE is a relatively common and life-threatening autoimmune disease in children and it triggers systemic organ damage, especially LN which is found more frequently (in about 70% of cases) in childhood-onset disease than in adult-onset SLE [9]. LN is one of the complications significantly impacting on prognosis, its treatment is crucial for improving the care of PSLE patients. In addition, proteinuria is an important risk factor for the progression of renal disease in patients with LN. Therefore, controlling proteinuria is particularly important in treating PLN [5].

TAC is a calcineurin inhibitor and the main immunophilin of TAC is FK-506-binding protein 12 (FKBP-12) in T cells. The complex of TAC and FKBP-12 inhibits calcineurin phosphatase, an essential enzyme for the activation of nuclear factor of activated T cells (NF-AT) [10]. NF-AT is an important transcription factor for the transcription of cytokine genes in T cells. Thus, TAC inhibits the transcription of T cell cytokines like interleukin-2 (IL-2) and interferon-γ (IFN-γ) [10]. TAC affects the growth and differentiation of

**Table 1.** Summary of clinical characteristics

| No. | Sex | Age (years) | Renal biopsies | TAC Dose (mg/d) | C3 (g/L) | | C4 (g/L) | | CH50 (U/ml) | | ESR (mm/h) | | PLT (10^9/L) | | 24 h Urine protein (g) | | PDN (mg/d) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Baseline* | *Last visit* | *Baseline* | *Last visit* | *Baseline* | *Last visit* | *Baseline* | *Last visit* | *Baseline* | *Last visit* | *Baseline* | *Last visit* | *Baseline* | *Last visit* |
| 1 | M | 9.2 | IV-G | 3 | 0.33 | 1.32 | 0.05 | 0.24 | 5 | 63 | 39 | 10 | 212 | 261 | 1.43 | 0.04 | 50 | 12.5 |
| 2 | M | 12.5 | V | 2 | 0.11 | 1.43 | 0.02 | 0.28 | 6 | 65 | 76 | 21 | 160 | 335 | 1.94 | 0.04 | 45 | 15 |
| 3 | M | 13 | V | 2-3 | 0.77 | 1.21 | 0.17 | 0.18 | 46 | 38 | 26 | 12 | 91 | 243 | 2.51 | 0.11 | 48 | 10 |
| 4 | F | 15.5 | IV-G | 2 | 1.1 | 1.32 | 0.24 | 0.22 | 40 | 48 | 17 | 7 | 179 | 249 | 2.62 | 0.08 | 45 | 10 |
| 5 | F | 14.5 | IV-G | 2-3 | 0.44 | 1.87 | 0.04 | 0.5 | 8 | 45 | 76 | 27 | 57 | 191 | 3.92 | 0.1 | 60 | 20 |
| 6 | F | 17.5 | III | 2-3 | 0.88 | 1.1 | 0.18 | 0.15 | 49 | 47 | 81 | 10 | 327 | 153 | 3.75 | 0.08 | 60 | 20 |
| 7 | F | 17 | IV-G | 2-3 | 0.88 | 0.99 | 0.19 | 0.21 | 50 | 46 | 24 | 7 | 143 | 180 | 5.3 | 0.32 | 60 | 12.5 |
| Mean | - | 14.17 | - | - | 0.64 | 1.32 | 0.13 | 0.25 | 29.14 | 50.29 | 48.43 | 13.43 | 167.00 | 230.29 | 3.07 | 0.11 | 52.57 | 14.29 |
| SD | - | 2.88 | - | - | 0.36 | 0.28 | 0.09 | 0.12 | 21.59 | 9.93 | 28.16 | 7.63 | 87.82 | 61.19 | 1.33 | 0.10 | 7.16 | 4.26 |

Baseline: before TAC treatment; last visit: treatment with TAC for 12 months; M: male; F: female.

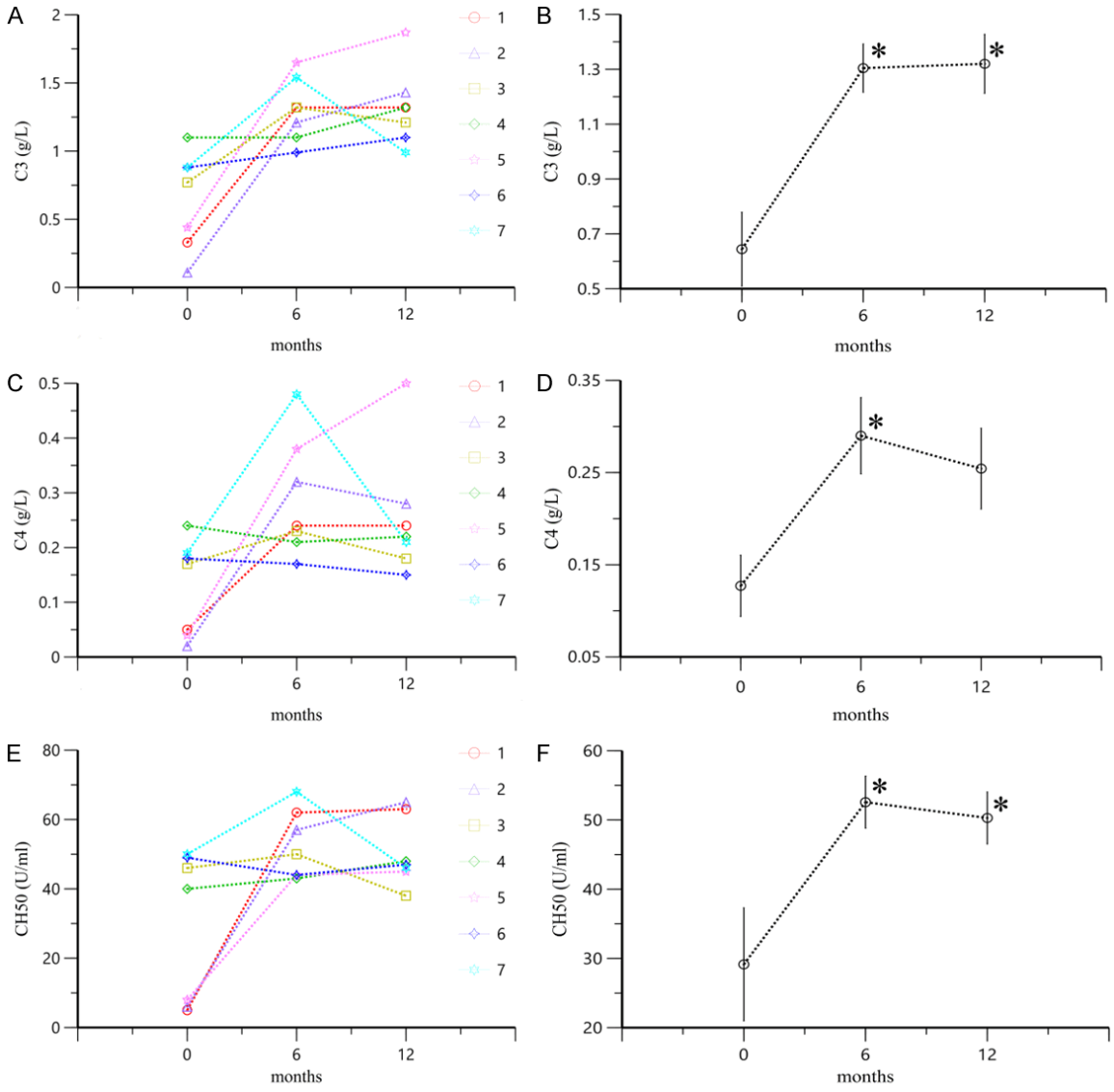


**Figure 1.** Changes in C3, C4, and CH50 after TAC treatment. A. Changes of C3 of every patient. B. Mean ± SE of C3. C. Changes of C4 of every patient. D. Mean ± SE of C4. E. Changes of CH50 of every patient. F. Mean ± SE of CH50. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. $^{*}P < 0.05$ vs. 0 month.

T-and B-lymphocytes, thereby, inhibiting immunity [11-13]. Until now, TAC has been used for renal transplant patients [14-19], liver transplant patients [20-25], lung transplant patients [26], idiopathic membranous nephropathy patients [27], nephritic syndrome patients [28], and systemic-onset juvenile idiopathetic arthritis patients [29]. In addition, TAC has been widely used in the treatment of SLE [7, 8, 30]. However, TAC research in PLN is very limited. The present study aims to investigate the effect of TAC in Chinese PLN patients.

In this study, seven Chinese PLN patients treating with TAC for 12 months were analyzed. Clinical characteristics were collected from the beginning of TAC treatment to the 12 month endpoint. TAC could increase C3, and CH50 level and decrease ESR level after treatment with TAC for 12 months. Significantly, TAC could ameliorate 24 h urine protein and reduce PDN dose in PLN. PLN patients undergo prolonged and repeated steroid therapy, increasing the risk of obesity, cushingoid appearance, osteoporosis, hypertension, infections, growth retardation and psychological problems. Moreover,

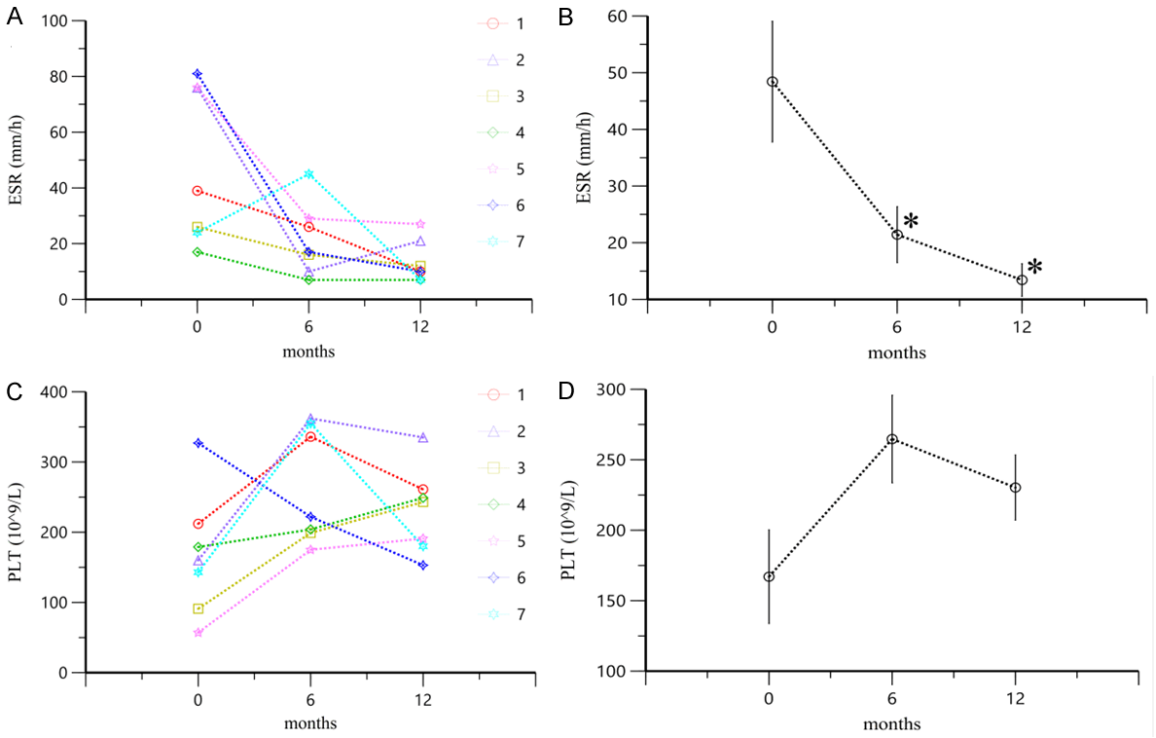


**Figure 2.** Changes in ESR and PLT after TAC treatment. A. Changes of ESR of every patient. B. Mean ± SE of ESR. C. Changes of PLT of every patient. D. Mean ± SE of PLT. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. $^{*}P < 0.05$ vs. 0 month.

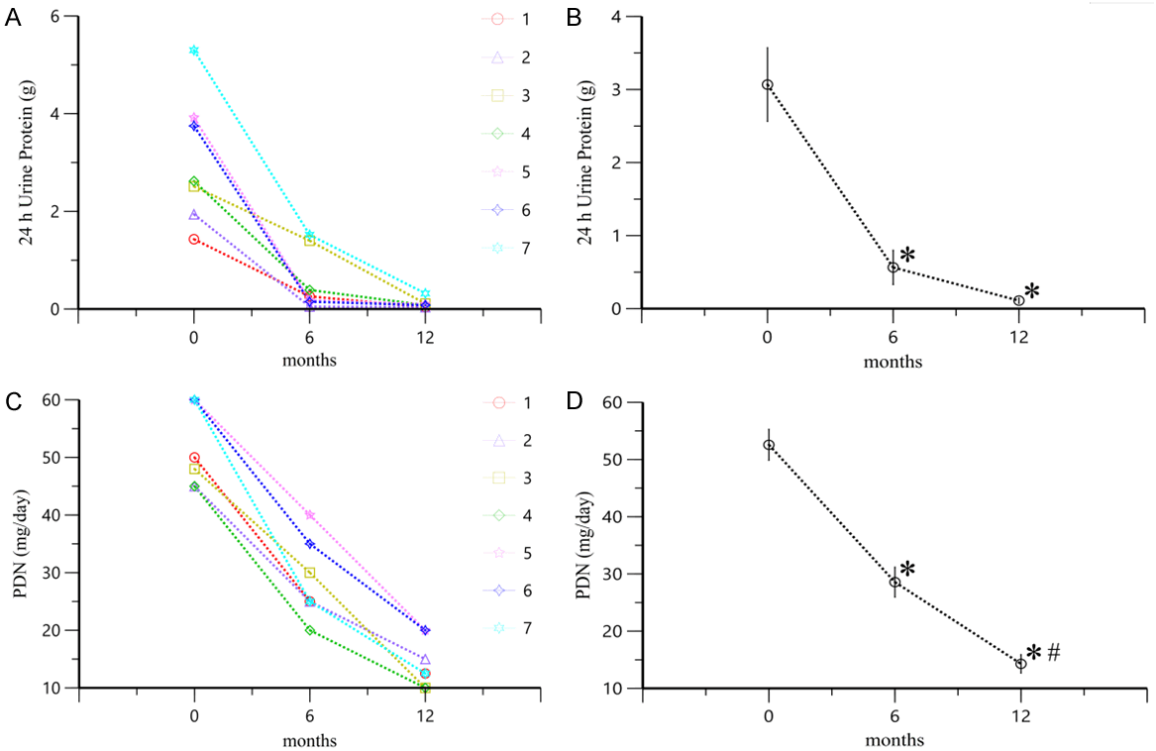


**Figure 3.** Changes in 24 hour urine protein and PDN dose after TAC treatment. A. Changes of 24 hour urine protein of every patient. B. Mean ± SE of 24 hour urine protein. C. Changes of PDN dose of every patient. D. Mean ± SE of PDN dose. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. $^{*}P < 0.05$ vs. 0 month, $^{\#}P < 0.05$ vs. 6 month.

proteinuria is an important risk factor for the progression of renal disease in PLN patients. Hence, TAC is a better choice of treatment in Chinese PLN by ameliorating 24 h urine protein and reducing PDN dose.

However, there are several limitations. First, it is a retrospective study. Second, it was only possible to include seven Chinese PLN patients. Therefore, further multicenter and prospective study with more Chinese PLN patients will be urgently needed.

In conclusion, TAC is a better choice of treatment in Chinese PLN by ameliorating 24 hour urine protein and reducing PDN dose.

## Acknowledgements

This work was supported by Clinical Pharmacy Key Specialty Construction Project of Shanghai (No. YZ2017/5), The Young Medical Talents of Wuxi (No. QNRC020), Young Project of Wuxi Health and Family Planning Research (No. Q201706), Wuxi Science and Technology Development Guidance Plan (medical and health care) (No. CSZON1744) and The AOSAIKANG pharmaceutical foundation (No. A201826).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Zhi-Ping Li, Department of Pharmacy, Children's Hospital of Fudan University, No. 399, Wanyuan Road, Minhang District, Shanghai 201102, China. Tel: (86)-021-64931224; Fax: (86)-021-64931224; E-mail: zplifudan@126.com

## References

[1] D'Cruz DP, Khamashta MA and Hughes GR. Systemic lupus erythematosus. Lancet 2007; 369: 587-596.

[2] Gurevitz SL, Snyder JA, Wessel EK, Frey J and Williamson BA. Systemic lupus erythematosus: a review of the disease and treatment options. Consult Pharm 2013; 28: 110-121.

[3] Rahman A and Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008; 358: 929-939.

[4] Takeuchi T, Tsuzaka K, Abe T, Yoshimoto K, Shiraishi K, Kameda H and Amano K. T cell abnormalities in systemic lupus erythematosus. Autoimmunity 2005; 38: 339-346.

[5] Hara R, Miyazawa H, Nishimura K, Momoi T, Nozawa T, Kikuchi M, Sakurai N, Kizawa T, Shimamura S, Yasuda S, Hiromura K, Sada KE, Kawaguchi Y, Tamura N, Takei S, Takasaki Y, Atsumi T and Mori M. A national survey on current use of mycophenolate mofetil for childhood-onset systemic lupus erythematosus in Japan. Mod Rheumatol 2015; 25: 858-864.

[6] Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, Font J, Gilboe IM, Houssiau F, Huizinga T, Isenberg D, Kallenberg CG, Khamashta M, Piette JC, Schneider M, Smolen J, Sturfelt G, Tincani A, van Vollenhoven R, Gordon C and Boumpas DT. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics. Ann Rheum Dis 2008; 67: 195-205.

[7] Kaieda S, Kobayashi T, Moroki M, Honda S, Yuge K, Kawano H, Mitsuyama K, Sata M, Ida H, Hoshino T and Fukuda T. Successful treatment of rectal ulcers in a patient with systemic lupus erythematosus using corticosteroids and tacrolimus. Mod Rheumatol 2014; 24: 357-360.

[8] Watanabe H, Yamanaka R, Sada KE, Zeggar S, Katsuyama E, Katsuyama T, Narazaki MT, Tatebe NT, Sugiyama K, Watanabe KS, Wakabayashi H, Kawabata T, Wada J and Makino H. The efficacy of add-on tacrolimus for minor flare in patients with systemic lupus erythematosus: a retrospective study. Lupus 2016; 25: 54-60.

[9] Carreno L, Lopez-Longo FJ, Monteagudo I, Rodriguez-Mahou M, Bascones M, Gonzalez CM, Saint-Cyr C and Lapointe N. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. Lupus 1999; 8: 287-292.

[10] Denton MD, Magee CC and Sayegh MH. Immunosuppressive strategies in transplantation. Lancet 1999; 353: 1083-1091.

[11] Dong QE, Fu R, Liu CY, Ruan EB, Wang XM, Wang GJ, Qu W, Liu H, Wu YH, Song J, Xing LM, Guan J, Li LJ, Wang HQ and Shao ZH. [Inhibitory effects of tacrolimus on effector T cells from patients with severe aplastic anemia]. Zhonghua Yi Xue Za Zhi 2013; 93: 1541-1545.

[12] Maguire O, Tornatore KM, O'Loughlin KL, Venuto RC and Minderman H. Nuclear translocation of nuclear factor of activated T cells (NFAT) as a quantitative pharmacodynamic parameter for tacrolimus. Cytometry A 2013; 83: 1096-1104.

[13] Yoshida T, Nakanishi K, Yoshioka T, Tsutsui Y, Maeda A, Kondo H and Sako K. Oral tacrolimus oil formulations for enhanced lymphatic delivery and efficient inhibition of T-cell's interleukin-2 production. Eur J Pharm Biopharm 2016; 100: 58-65.

[14] Andreu F, Colom H, Grinyo JM, Torras J, Cruzado JM and Lloberas N. Development of a population PK model of tacrolimus for adaptive dosage control in stable kidney transplant patients. Ther Drug Monit 2015; 37: 246-255.
[15] Benkali K, Rostaing L, Premaud A, Woillard JB, Saint-Marcoux F, Urien S, Kamar N, Marquet P and Rousseau A. Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in renal transplant recipients on a new once-daily formulation. Clin Pharmacokinet 2010; 49: 683-692.
[16] Bergmann TK, Hennig S, Barraclough KA, Isbel NM and Staatz CE. Population pharmacokinetics of tacrolimus in adult kidney transplant patients: impact of CYP3A5 genotype on starting dose. Ther Drug Monit 2014; 36: 62-70.
[17] Han N, Ha S, Yun HY, Kim MG, Min SI, Ha J, Lee JI, Oh JM and Kim IW. Population pharmacokinetic-pharmacogenetic model of tacrolimus in the early period after kidney transplantation. Basic Clin Pharmacol Toxicol 2014; 114: 400-406.
[18] Zhao W, Elie V, Roussey G, Brochard K, Niaudet P, Leroy V, Loirat C, Cochat P, Cloarec S, Andre JL, Garaix F, Bensman A, Fakhoury M and Jacqz-Aigrain E. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. Clin Pharmacol Ther 2009; 86: 609-618.
[19] Zuo XC, Ng CM, Barrett JS, Luo AJ, Zhang BK, Deng CH, Xi LY, Cheng K, Ming YZ, Yang GP, Pei Q, Zhu LJ, Yuan H, Liao HQ, Ding JJ, Wu D, Zhou YN, Jing NN and Huang ZJ. Effects of CYP3A4 and CYP3A5 polymorphisms on tacrolimus pharmacokinetics in Chinese adult renal transplant recipients: a population pharmacokinetic analysis. Pharmacogenet Genomics 2013; 23: 251-261.
[20] Lu YX, Su QH, Wu KH, Ren YP, Li L, Zhou TY and Lu W. A population pharmacokinetic study of tacrolimus in healthy Chinese volunteers and liver transplant patients. Acta Pharmacol Sin 2015; 36: 281-288.
[21] Musuamba FT, Guy-Viterbo V, Reding R, Verbeeck RK and Wallemacq P. Population pharmacokinetic analysis of tacrolimus early after pediatric liver transplantation. Ther Drug Monit 2014; 36: 54-61.
[22] Wallin JE, Bergstrand M, Wilczek HE, Nydert PS, Karlsson MO and Staatz CE. Population pharmacokinetics of tacrolimus in pediatric liver transplantation: early posttransplantation clearance. Ther Drug Monit 2011; 33: 663-672.
[23] Yang JW, Liao SS, Zhu LQ, Zhao Y, Zhang Y, Sun XY, Rao W, Qu W, Li WZ and Sun LY. Population pharmacokinetic analysis of tacrolimus early after Chinese pediatric liver transplantation. Int J Clin Pharmacol Ther 2015; 53: 75-83.
[24] Zhang XQ, Wang ZW, Fan JW, Li YP, Jiao Z, Gao JW, Peng ZH and Liu GL. The impact of sulfonylureas on tacrolimus apparent clearance revealed by a population pharmacokinetics analysis in Chinese adult liver-transplant patients. Ther Drug Monit 2012; 34: 126-133.
[25] Zhu L, Yang J, Zhang Y, Jing Y, Zhang Y and Li G. Effects of CYP3A5 genotypes, ABCB1 C3435T and G2677T/A polymorphism on pharmacokinetics of Tacrolimus in Chinese adult liver transplant patients. Xenobiotica 2015; 45: 840-846.
[26] Monchaud C, de Winter BC, Knoop C, Estenne M, Reynaud-Gaubert M, Pison C, Stern M, Kessler R, Guillemain R, Marquet P and Rousseau A. Population pharmacokinetic modelling and design of a Bayesian estimator for therapeutic drug monitoring of tacrolimus in lung transplantation. Clin Pharmacokinet 2012; 51: 175-186.
[27] Di J, Qian Q, Yang M, Jiang Y, Zhou H, Li M and Zou Y. Efficacy and safety of long-course tacrolimus treatment for idiopathic membranous nephropathy. Exp Ther Med 2018; 16: 979-984.
[28] Wang DD, Chen X and Li ZP. Efficacy and safety of tacrolimus in treating pediatric refractory nephrotic syndrome: a meta-analysis. Int J Clin Exp Med 2018; 11: 6436-6444.
[29] Wang D, Chen X and Li Z. Treatment of patients with systemic-onset juvenile idiopathic arthritis with tacrolimus. Exp Ther Med 2019; 17: 2305-2309.
[30] Wang DD, Lu JM, Li Q and Li ZP. Population pharmacokinetics of tacrolimus in paediatric systemic lupus erythematosus based on real-world study. J Clin Pharm Ther 2018; 43: 476-483.