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REVIEW

Off-label use of tacrolimus in children with glomerular disease: Effectiveness, safety and pharmacokinetics

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Glomerular diseases are leading causes of end-stage renal disease in children. Tacrolimus is frequently used off-label in the treatment of glomerular diseases. The effectiveness, safety and pharmacokinetic data of tacrolimus in the treatment of glomerular diseases in children are reviewed in this paper to provide evidence to support its rational use in clinical practice. The remission rates in previously published studies were different. In 19 clinical trials on children with nephrotic syndrome, the overall remission rate was 52.6-97.6%. In four clinical trials on children with lupus nephritis, the overall remission rate was 81.8-89.5%. In a pilot study with paediatric Henoch-Schönlein purpura nephritis patients, the overall remission rate was 100.0%. Infection, nephrotoxicity, gastrointestinal symptoms and hypertension are the most common adverse events. Body weight, age, *CYP3A5* genotype, cystatin-C and daily dose of tacrolimus may have significant effects on the pharmacokinetics of tacrolimus in children with glomerular disease. More prospective controlled trials with long follow-up are needed to demonstrate definitely the effectiveness, safety and pharmacokinetics of tacrolimus in children with glomerular diseases.

KEYWORDS
children, glomerular disease, tacrolimus

1 | INTRODUCTION

Tacrolimus was first isolated in 1984 from the culture broth of *Streptomyces tsukubaensis*, a soil microorganism found in Mount Tsukuba, Japan.[1] It was initially named FK506, formally named tacrolimus and then commercially called Prograf. Tacrolimus belongs to the family of 23-membered ring macrolides, with a molecular weight of 822 Daltons.[2,3] Tacrolimus was listed in Japan as a liver transplant drug in 1993 and was approved in the United States by the Food and Drug Administration in 1994 to prevent graft rejection after liver and kidney transplantation, or to treat graft rejection that cannot be controlled by other immunosuppressive drugs after liver or kidney transplantation. As a calcineurin inhibitor (CNI), tacrolimus is currently widely used as a cornerstone

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immunosuppressant given to solid-organ transplant recipients for prophylaxis or treatment of graft rejection after transplantation.

Tacrolimus is frequently used off-label in the treatment of glomerular diseases, especially refractory glomerular diseases.[4,5] Glomerular diseases are a group of kidney diseases that mainly involve renal glomerular lesions with clinical manifestations of haematuria, proteinuria, oedema, hypertension and other similar symptoms. Glomerular disease is a common cause of kidney disease in children.[6] If it cannot be treated or controlled quickly and effectively, it can develop into chronic renal insufficiency, which is the one of the main causes of irreversible end-stage renal disease (ESRD) and seriously endangers children's health.[7,8]

The uniquely strengthening and maturing immune system during childhood may require age-specific approaches to disease management.[9] In paediatric clinical practice, off-label use of tacrolimus is also a common issue. Tacrolimus has not yet been reviewed in the treatment of glomerular diseases in children. The objectives of the present study were to examine the effectiveness, safety and clinical pharmacokinetics of tacrolimus in children with glomerular diseases.

1.1 | Action mechanism of tacrolimus

The aetiology and mechanism of glomerular diseases are very complex. Infections, drugs, heredity, environment and other factors can be involved. The immune system and the kidneys are closely linked.[10] In the 1920s, Esherich first proposed that immune abnormality is one of the important pathogenesis of glomerular diseases. After nearly 100 years of research, immune-mediated damage to glomerular structures is considered largely responsible for the pathology associated with most glomerular diseases.[11,12]

Immunosuppressive agents play an important role in the treatment of glomerular diseases. However, there is currently no unified treatment because of the diversity of clinical manifestations and pathological types of glomerular diseases, and the variety of immunosuppressive agents. The use of immunosuppressive agents in children with glomerular diseases usually includes induction remission, maintenance remission and treatment of relapse, which takes a long time. An inadequate course or dose of immunosuppressive therapy may increase the risk of treatment failure or recurrence, but overuse of immunosuppressive agents may increase the risk of infection, tumours, liver and kidney damage, and bone marrow suppression. A reasonable immunosuppressive therapy is therefore the key to relieving symptoms, improving prognosis and protecting children's renal functions.

Glucocorticoids are used as first-line drugs in the treatment of immune-mediated glomerular diseases, but glucocorticoid resistance is often seen in the treatment of glomerular diseases associated with massive proteinuria. Large doses and long-term use of glucocorticoids can cause serious adverse reactions, including hypertension, growth disorders, osteoporosis, hirsutism and behavioural problems. In 2012, the Kidney Disease: Improving Global Outcomes guidelines for glomerulonephritis recommended CNI as an initial treatment alternative for membranous nephropathy. CNI was also recommended for lupus nephritis (LN) treatment.[13] The 2016 Chinese guideline for Henoch–Schönlein purpura nephritis (HSPN) indicates that glucocorticoids combined with CNI can be used to treat HSPN.

The immunosuppressive mechanism of tacrolimus is similar to that of cyclosporine (cyclosporin A, CsA). However, its potent immunosuppressive effect is 100 times stronger by weight than that of CsA.[14] Tacrolimus exerts immunosuppressive effects by binding to its cytoplasmic protein receptor, **FK506-binding protein 12** (FKBP12), to form a new complex (FKBP12–FK506 complex) that interacts with and inhibits calcineurin in T lymphocytes, preventing the dephosphorylation of nuclear factor of activated T cells, ultimately inhibiting interleukin-2 (IL-2) transcription and T lymphocyte signal transduction.[15] Tacrolimus has been found to not only inhibit the activation of T cells, but also T helper T cells (Th2), thereby reducing the production of IL-10, which induces B cells to produce large amounts of autoantibodies.[16] Tacrolimus can inhibit mediator release from basophils and mast cells.[17] Both cellular and humoral immunities are inhibited to reduce the damage to the kidney caused by the inflammatory response. Tacrolimus' pivotal mechanism of action involves inhibition of the redistribution of calcineurin at the slit diaphragm.[18]

In recent years, podocyte injury has been recognized as a central event in the occurrence and progression of glomerular diseases.[19] Podocytes are highly differentiated cells with limited proliferative and divisive abilities, which are difficult to regenerate and repair after injury. Podocytes are located outside the glomerular basement membrane, which constitutes the glomerular filtration barrier together with vascular endothelial cells. Normally, soluble small molecules and water in plasma can easily pass through the barrier, while large molecules such as albumin are restricted. Podocytes are the outermost part of the glomerular filtration barrier, which is the last barrier to prevent protein loss. Changes in podocyte function or structure lead to changes in the permeability of the glomerular filtration barrier, resulting in proteinuria in patients, which is the main reason for the occurrence and progress of various glomerular diseases. When podocytes are severely injured, they can be detached from the basement membrane of the glomerulus and the number of podocytes decreases, which can lead to glomerulosclerosis and eventually renal failure.[20] Tacrolimus also protects podocytes and rapidly reduces proteinuria.[21]

Although tacrolimus is used off-label in the treatment of glomerular diseases, off-label use should not be off-knowledge. Evidence is still needed to support the rational use of tacrolimus in children with glomerular disease. However, there is no relevant review. Thus, in this paper, the effectiveness, safety and pharmacokinetic data of tacrolimus in the treatment of glomerular diseases in children were reviewed to provide evidence to support its rational use in clinical practice.

1.2 | Effectiveness

1.2.1 | Nephrotic syndrome

Nephrotic syndrome is one of the most common manifestations of glomerular disease in children with clinical manifestations of proteinuria, hypoalbuminemia, hyperlipidaemia and oedema.[24,25] Primary nephrotic syndrome accounts for about 90% of all nephrotic syndromes in childhood. Oral glucocorticoids have been recognized as the first-line treatment for primary nephrotic syndrome. Minimal change nephropathy (MCN) is the most common pathological change in the nephrotic syndrome in children, and it was reported that more than 90% of children with MCN could achieve remission with oral corticosteroids therapy.[26] However, relapses are common, resulting in increased morbidity, complications and cost of treatment, and decreased quality of life.[27] In addition, most children with the second most common histological subtype, focal segmental glomerulosclerosis (FSGS), did not respond to corticosteroids.[28] The current research hotspot explores the the treatment for these refractory nephrotic syndromes.

Immunosuppressive agents mainly used in the treatment of nephrotic syndrome in children include mycophenolate mofetil, CsA and tacrolimus. Cyclophosphamide (CTX) has been the first choice for the treatment of refractory nephrotic syndrome in children. However, due to its adverse reactions, such as hepatotoxicity, CTX has been seldom used in clinical practice.[29] Tacrolimus is also commonly used in clinical practice for the off-label treatment of nephrotic syndrome. Its application in nephrotic syndrome was first used in adults in the 1990s and in paediatric patients in the 2000s.[30-33] Tacrolimus has become an important drug in the treatment of nephrotic syndrome because of its higher effectiveness and fewer side effects compared to CsA.[34,35] Table 1 lists the published reports of tacrolimus therapy in paediatric nephrotic syndrome. Nineteen studies evaluated the effectiveness of tacrolimus in children with nephrotic syndrome, four of which were randomized control studies.

Tacrolimus is used for treatment of steroid-resistant nephrotic syndrome (SRNS), steroid-dependant nephrotic syndrome or frequently relapsing nephrotic syndrome. Glucocorticoids are the most commonly used concomitant medication with an initial high dose followed by a gradual tapering off. The complete remission rate is 40-97.6% and the overall remission rate (the sum of the complete remission rate and the partial remission rate) is 52.6-97.6%. The mean follow-up time is 18.2 months, ranging from 2.5 to 111 months. The initial dose of tacrolimus is mostly 0.1 mg/kg/d, twice daily. In ten clinical trials, the dosage of tacrolimus was adjusted according to the target trough concentration (C_0). The range of tacrolimus target C_0 used in four trials was 5-10 ng/mL. In the other six studies, the highest target C_0 was 7-15 ng/mL and the lowest was 3-5 ng/mL.

1.2.2 | Lupus nephritis

Lupus nephritis (LN) is a representative tissue disorder of systemic lupus erythematosus (SLE).[52] Worldwide, LN occurs in about 50–80% of paediatric-onset SLE, which frequently develops in the early stages of SLE.[53,54] LN seriously affects the survival rate of patients with SLE.[55] The major characteristic feature of paediatric-onset LN is acute inflammatory renal damage, which suggests that the use of immunosuppressants in the early stages of childhood LN may improve the prognosis of later stages.[56-58]

Glucocorticoids in combination with CTX are currently a classic treatment for LN.[59] However, severe adverse reactions have also increased, such as amenorrhea, atypical hyperplasia of the cervix, leukocyte decline, infection and alopecia caused by CTX, and especially the obviously toxic effects of gonads.[60] The exploration of new immunosuppressive agents for the treatment of LN to improve the efficacy and reduce side effects is a common concern in basic and clinical research studies.

The pathogenesis of LN is not completely clear. It is initially believed that activation of T and B cells produces the deposition of excessive autoantibodies, a variety of cytokines, inflammatory cytokines and immune complexes, which damages the kidneys. While tacrolimus inhibits both cellular and humoral immunities, it can also inhibit the maturation of dendritic cells, which play an important role in the pathogenesis of LN.[61,62] As early as 1993, Entani et al observed the effects of tacrolimus in 13 mice with advanced LN.[63] Each mouse was administered 1 mg/kg per day for 8 weeks with 9 mice as a blank control group. The results showed that urine protein significantly decreased, serum urea nitrogen decreased and anti-dsDNA was negative in the experimental group. A pathological examination showed that cell proliferation and crescent formation were inhibited, and deposition of C3 was also significantly reduced, suggesting that tacrolimus can control the progression of LN and provide the basis for clinical research.[63]

The use of tacrolimus in children with lupus nephritis was reported in two case reports and four clinical trials.[64-69] Tanaka et al observed 19 patients with childhood-onset LN who took tacrolimus at a dose of 3 mg/d (0.03-0.075 mg/kg/d) once a day (the trough blood concentration at 12 h was about 4.0 ng/mL) for an average of 42 months.[66] Of the 19 patients treated, 17 (89%) had no significant adverse reactions and maintained remission. An open-label pilot study reported that five of six young patients with paediatric-onset, long-standing LN with tacrolimus once a day were judged as showing complete remission after 6 months of treatment, while the remaining patient was judged to show partial remission.[67] The efficacy of mizoribine–tacrolimus-based induction therapy was studied in seven cases of paediatric LN.[68] Complete remission was achieved in four patients (56%), while partial remission was achieved in two patients (29%) at the end of the 12-month treatment period. A marked histologic improvement was confirmed in two patients who underwent post-treatment renal biopsy. After a mean of 18 months of treatment with tacrolimus in 11 young patients with LN, complete remission was achieved in eight patients (73%) and partial remission was achieved in two patients (17%).[69]

TABLE 1 Published reports of tacrolimus therapy in paediatric nephrotic syndrome

Ref.	No. (TAC group)	Clinical features	Control	Dose (mg/kg/d)	Target C_0 (ng/mL)	Concomitant drugs	Follow-up (m)	Results (-No.)
Loeffler et al[33]	16							Treatment-resistant NS
No	0.1	5-10	Steroids	6.5*		(2.5-18)	CR-13; PR-2	
Bhimma et al[36]	20	SRNS (FSGS)	No	0.2-0.4	7-15	Steroids, ACEI or FA or VCX or LLA	27.5* (13.7-43.7)	CR-8; PR-9
Xia et al[37]	12	NS	No	0.1-0.15	...	Steroids	17-50	CR-8
Gulati et al[38]	22	SRNS	No	0.1	5-10	Steroids	9.7 ± 4.2	CR-16; PR-2; lost:3 for ADE
Choudhry et al[39]	21	SRNS	CsA (RCT)	0.1-0.2	...	Steroids, ACEI	12	CR-10; PR-8
Butani et al[40]	16	SRNS	No	0.05-0.2	5-10	Steroids, ARB or ACEI	22#	CR-15
Roberti et al[31]	19	SRNS	No	0.1	5-8	NM	55 *(17-111)	CR + PR-10; lost:1
Wang et al[41]	SRNS:26; FRNS/SDNS:24	FRNS, SDNS, SRNS	CsA	0.05-0.15	5-12	Steroids	24	SRNS: CR-22; PR-4; FRNS/SDNS: CR-22; PR-1
Gulati et al[42]	66	SRNS	CsA (RCT)	0.12 ± 0.03,	...	Steroids, ACEI	12	CR-33; PR-19; lost: 4
Supavekin et al[43]	SRNS:9; SDNS:9;	SDNS, SRNS	No	0.03-0.2.	...	Steroids	37.2* (2.4-76.8)	SRNS: CR-4 SDNS: CR-9
Kim et al[44]	SSNS:23; SRNS:22	SSNS, SRNS	MMF, RTX, CsA, CTX	0.1	3-5	ARB and/or ACEI	SSNS: 31.7*; SRNS: 20.5*	SSNS: CR-18; PR-4; SRNS: CR-12; PR-5
Jahan et al[45]	25	SRNS	No	0.10-0.19		ARB or ACEI	14 (6-18)	CR-16
Shah et al[46]	42	SRNS	No	0.05-0.1	...	Steroids	6	CR-41; PR-1
Yang et al[32]	SDNS:44; SRNS:33	SDNS, SRNS	No	0.1-0.2	5-10	Steroids	12	SDNS: CR-34; PR-6; SRNS: CR-13; PR-10
Hussain Shah et al[47]	43	SRNS	No	NM	...	Steroids	6	CR-40; PR-3
Shah et al[48]	42	SRNS	CsA	0.1-0.2	...	Steroids	6	CR-41; PR-1
Wang et al[49]	38	FRNS or SDNS	MMF	0.05-0.15	...	Steroids	12	CR-31; PR-3; lost:2 for ADE
Sinha et al[50]	31	SRNS	MMF (RCT)	NM	4-7	Steroids	12	CR-23; PR-5
Basu et al[51]	60	MCN, FSGS	RTX (RCT)	0.2	5-7	Steroids	12	CR-38

Data were summarized by mean ± standard deviation (SD) or median (range). *Mean; #median.

Complete remission (CR) was defined as the absence of proteinuria, including a urine protein/creatinine ratio (UP/C) less than 0.2 g/g, or negative results of a urine albumin test by dipstick for three consecutive days, or proteinuria <4 mg/h per m^2 body surface area (BSA).

Partial remission (PR) was defined as subnephrotic proteinuria (0.2 ≤ UP/C < 2), or at least 50% reduction from proteinuri baseline before treatment, or proteinuria reduction to 4.1-40 mg/h per m^2 BSA, or urine protein on +2 on urine dipstick.

Non-response (NR) was persistent nephrotic-range proteinuria (Up/Uc ratio > 2 g/g), or proteinuria reduction <50%, or proteinuria >40 mg/h per m^2 BSA, or patient still having +3 urine proteins on urine dipstick.

ACEI, angiotensin-converting enzyme inhibitor; ADE, adverse drug event; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; C_0, trough concentration; CsA, cyclosporin A; CPM, cyclophosphamide; CR, complete remission; CTX, cyclophosphamide; FA, folic acid; FRNS, frequent-relapse nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; LLA, lipid lowering agents; m, month; MCN, minimal change nephropathy; MMF, mycophenolate mofetil; NM, not mentioned; No., number; NR, non-response; NS, nephrotic syndrome; PR, partial remission, RCT, randomized controlled trial; RTX, rituximab; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; TAC, tacrolimus; VCX, vitamin complex.

1.2.3 | Henoch–Schönlein purpura nephritis

Henoch–Schönlein purpura (HSP), an immunoglobulin A (IgA)-mediated systemic small-vessel vasculitis, is the most common vasculitis in children.[70] HSPN is the principal cause of morbidity for HSP and 1-7% of HSPN patients may progress to renal failure or ESRD.[71]

Immunosuppressive therapy has become the standard treatment in children with HSPN.[72-78] Tacrolimus has also been recently suggested in the treatment of HSPN in children.[79] A case of HSPN successfully treated with multi-target therapy using tacrolimus was reported in children.[79] It was indicated that tacrolimus may be a promising steroid-sparing agent for treatment of severe HSP nephritis. In a pilot study with 20 paediatric HSPN patients in our centre, 12 patients reached complete remission and eight patients reached partial remission at the end of 6-month treatment of tacrolimus.[80]

1.3 | Adverse events

Adverse drug events were reported in 14 of 19 trials in Table 1. In 14 studies with data on adverse drug events, five people quit because of adverse drug events. A total of 196 adverse drug events was reported. In these 196 adverse drug events, the number of infections (including severe and mild infection) was the highest, accounting for 56 cases (28.6%). Nephrotoxicity (14.3%), gastrointestinal symptoms (14.3%) and hypertension (14.3%) were common. The number and proportion of adverse drug events are shown in Table 2.

Of these 14 studies, the follow-up time (or median, mean) in eight studies was less than or equal to 12 months, and a total of 109 adverse drug events were reported. Mild infection (n = 27), nephrotoxicity (n = 17), glucose abnormality (n = 14) and hypertension (n = 12) were the most common adverse drug events. In the remaining six studies with a follow-up of more than 12 months, 87 adverse drug events were observed. Severe infection (n = 19), gastrointestinal symptoms (n = 18), hypertension (n = 16) and nephrotoxicity (n = 11) were the most common adverse drug events.

The burning issue with tacrolimus is its nephrotoxicity, which hinders the use of the drug in exigency of proper dosage management.[81] Morgan et al reported the first histological data concerning tacrolimus nephrotoxicity in childhood nephrotic syndrome.[82] Another study suggested that one-quarter of children with SRNS showed histological evidence of nephrotoxicity following prolonged therapy with CsA or tacrolimus, and the risk of toxicity was increased for patients with initial resistance, persistent hypertension and nephrotic-range proteinuria.[83]

Some other adverse reactions are also reported in the treatment of glomerular diseases, eg tacrolimus-induced diabetic ketoacidosis was reported in a 12-year-old girl with SRNS,[84] while acute renal failure secondary to tacrolimus-induced haemolytic uremic syndrome was found in a child with nephrotic syndrome.[85]

TABLE 2 Number and proportion of adverse drug events in clinical studies of tacrolimus in the treatment of nephrotic syndrome in children

	Classification	Frequency	Ratio (%)
1	Severe infection	29	14.8
2	Gastrointestinal symptoms	28	14.3
3	Nephrotoxicity	28	14.3
4	Hypertension	28	14.3
5	Mild infection	27	13.8
6	Glucose abnormality	17	8.7
7	Neurological symptoms	10	5.1
8	Liver dysfunction	10	5.1
9	Anaemia	8	4.1
10	Oedema	3	1.5
11	Psychiatric symptoms	2	1.0
12	Cataract	2	1.0
13	Lymphoma	1	0.5
14	Polytrichosis	1	0.5
15	Electrolyte disturbance	1	0.5
16	Leukopenia	1	0.5
	Total	196	100.0

*These adverse drug event data were collected from 14 studies.[31,32,36-42,47-50,66]

1.4 | Pharmacokinetics

The oral absorption of tacrolimus is incomplete and individual differences are large.[86] Its absorption is mainly in the small intestine and the relative bioavailability is significantly affected by food.[87] Whereas absorption is highest in a fasting state, high-fat and carbohydrate meals reduce the mean area under the curve (AUC) and maximum blood concentrations. Tacrolimus primarily redistributes to erythrocytes. The whole-blood concentrations are 10-30 times higher than plasma concentrations.[88] It is 99% bound to plasma protein, primarily to albumin and an acute-phase protein, α1-acid glycoprotein. It is almost completely metabolized by **CYP3A4** and CYP3A5 in the liver, and is a substrate of the **P-glycoprotein** (P-gp) encoded by the multidrug-resistance 1 gene (*ABCB1*).[89] Studies have shown that CYP3A5 is the predominant enzyme in the metabolism of tacrolimus, with CYP3A4 contributing, but having a lower efficiency for catalysis.[90,91] Tacrolimus is primarily eliminated via biliary excretion after metabolization.

The recommended target C_0 for children with nephrotic syndrome is 5-10 ng/mL,[32,33] which is lower than 10-20 ng/mL during the immediate post-transplantation period used for all types of paediatric organ transplantations.[92] The target C_0 and $AUC_{0\text{-}12\ h}$ level for treatment remission are higher than those in relapse in children with SRNS.[45]

In the first population pharmacokinetic model of tacrolimus in children with nephrotic syndrome, body weight, *CYP3A5* genotype had significant impact on tacrolimus pharmacokinetics.[93] The mean clearance/bioavailability (CL/F) of tacrolimus is in agreement with previously reported values of tacrolimus in paediatric kidney transplant patients.[94] However, tacrolimus appeared to have a much shorter half-life in paediatric nephrotic syndrome patients (about 9 h) than in children receiving kidney transplants (about 24 h). In another two population pharmacokinetic models of tacrolimus in children with nephrotic syndrome, weight, age, cystatin-C and daily dose of tacrolimus could partly explain the interindividual variability in the CL/F of tacrolimus.[95,96] Population characteristics, population pharmacokinetics parameters, Inter-individual variabilities and population pharmacokinetics equations in these studies are included in Table 3.

In the in vitro experiment, liver and kidney microsomes from donors with a *CYP3A5*1/*3* genotype had a higher tacrolimus clearance compared with *CYP3A5*3/*3* microsomes.[90] The population pharmacokinetic model of tacrolimus in children with nephrotic syndrome demonstrated that the weight-normalized CL/F of tacrolimus was significantly higher in expressers (*CYP3A5*1* allele) than in non-expressers (*CYP3A5*3/*3*). The CL/F in *CYP3A5*1* carriers was 1.6 times higher than that in *CYP3A5*3/*3* carriers. Similarly, the rates in paediatric and adolescent kidney transplant recipients were 1.45, 1.66 and 1.8, respectively.[97-99] In children with HSPN, the dose-adjusted trough concentration of children with *CYP3A5*1* allele was significantly higher than that of children with *CYP3A5*3/*3* genotype.[80]

2 | DISCUSSION

Tacrolimus may exert a favourable effect against the progression of glomerular lesions. A review concluded that tacrolimus was more effective than CTX, mycophenolate mofetil, leflunomide, nitrogen mustard benzoate or azathioprine.[4] However, the evidence-based clinical data are still limited. The above research cases comprise few patients with short observation times and differing research programmes and rates of remission. Strict, prospective controlled trials in paediatric glomerular disease are generally limited, therefore the long-term efficacy and safety of tacrolimus in the treatment of glomerular diseases needs further follow-up observation and summary analyses.

The remission rate differed in each study. One possible reason for this finding is the difference in the proportion of pathological

TABLE 3 Population pharmacokinetic parameters of final models of tacrolimus in children with glomerular disease

	Hao et al[93]	Wang et al[95]	Wang et al[96]
No. of patients	28	65	41
Male/female	19/9	44/21	32/9
Age (year) (mean ± SD)	9.5 ± 4.4	7.6 ± 3.9	8.05 ± 3.68
Weight (kg) (mean ± SD)	36.5 ± 17.4	30.85 ± 17.12	30.53 ± 13.51
Samples (n)	148	147	96
Compartment model	One	One	One
Typical values			
K_a (h^{-1})	5.21	4.48 (fixed)	4.5 (fixed)
CL/F (L/h)	30.9	5.46	17.7
V/F (L)	411	57.1	314 (fixed)
Inter-individual variability (%)			
K_a	79.1	…	…
CL/F	43.8	22.2	31.1
V/F	99.4	0.2	…
Residual variability (%)	25.9*	35.9*	122.5#
PPK equation			
CL/F	$CL/F = 30.9 \times (WT/70)^{0.75} \times F_{CYP3A5}$; if CYP3A5 *1/*1 and CYP3A5 *1/*3, $F_{CYP3A5} = 1.60$; if CYP3A5 *3/*3, $F_{CYP3A5} = 1$	$CL/F = 5.46 \times EXP(0.0323 \times age) \times EXP(-0.359 \times cystatin\text{-}C) \times EXP(0.148 \times daily\ dose\ of\ TAC)$.	$CL/F = 17.7 \times (WT/70)^{0.75} \times (age/8.30)^{-0.26}$

CL, clearance; EXP, exponential function; Ka, absorption rate constant; SD, standard deviation; V, volume of distribution.
*Exponential error; #additive error.

types of patients with glomerular disease in the various studies. According to the pathology, glomerular disease can be divided into minimal-change disease (MCD), FSGS, diffuse glomerulonephritis (including membranous nephropathy, mesangioproliferative glomerulonephritis and so on), IgA nephropathy and unclassified glomerulonephritis. The clinical manifestations of various glomerular diseases differ, but proteinuria is a major clinical manifestation of most glomerular diseases.[100] Proteinuria is an independent risk factor for the progression of kidney disease[101]; if no active intervention and treatment is taken, it will eventually lead to ESRD. In recent years, studies have found that the mutation, deletion and abnormal expression of podocyte proteins, especially nephrin and podocin, play an important role in glomerulopathy and proteinuria.[102-104] Tacrolimus's mechanism that protects glomerular podocytes and reduces urinary protein may be associated with up-regulation of nephrin and podocin expression.[105,106] However, the expression changes of these podocyte proteins in different pathological types of glomerular diseases are inconsistent.[107,108] Another possible reason for different remission rates in different studies is whether the relapses of glomerular disease has been observed. Patients treated with tacrolimus suffer from a high rate of relapses when the drugs are reduced or discontinued.[109] Studies observed for ≤6 months may not demonstrate relapses of the glomerular diseases.

Although the efficacy and safety data of tacrolimus in paediatric patients with glomerular disease are available, its narrow therapeutic index and high intra- and inter-individual pharmacokinetic variability still hinder its clinical application.[110,111] Both underexposure and overexposure to tacrolimus may have serious consequences in terms of an increased risk of treatment failure or toxic side effects.[112]

The majority of pharmacogenetic studies on tacrolimus and CsA have focused on the effects of variants in the *CYP3A4*, *CYP3A5* and *ABCB1* genes because of the central role the enzymes and transporters that they code for play in tacrolimus and CsA deposition. However, no study has shown significant correlation between *CYP3A4* gene polymorphism and tacrolimus pharmacokinetics in children, and the impact of ABCB1 single-nucleotide polymorphism on tacrolimus paediatric pharmacokinetics is still controversial. Instead, *CYP3A5* gene polymorphism has been reported to significantly affect tacrolimus pharmacokinetic and clinical outcomes in solid-organ transplantation patients.[113-118] Increasing evidence supports a potential benefit for CYP3A5 genotyping before beginning a tacrolimus-based immunosuppressive treatment in children who had organ transplants.[89,119]

As a possible association exists between CYP3A5 polymorphism and tacrolimus CL, a CYP3A5 genotype-based dosing regimen in treatment of glomerular disease should be recommended.[120] However, the liver enzymes activity of solid organ transplant patients showed moderate disturbance during tacrolimus treatment due to hypohepatia and/or rapid change of renal function after transplant.[121] It was reported that the clearance of tacrolimus was affected by the post-transplantation time in days, haematocrit, liver weight and liver function.[122-125] These pharmacokinetics data assessed in paediatric organ transplant patients may not be directly used in paediatric patients with glomerular disease.[126] Paediatric patients with glomerular disease may have hypoproteinaemia.[45,127] Intestinal oedema caused by hypoproteinaemia may affect tacrolimus absorption. What's more, hypoalbuminemia may reduce protein binding and thereby alter clearance or volume of distribution. Tacrolimus is highly bound to plasma proteins.[128] The proportion of free tacrolimus in patients with glomerular disease will be higher than that in patients with renal transplantation,[129] therefore compared with transplant patients, patients with glomerular diseases have lower volume of distribution and higher clearance. The pharmacokinetic characteristics of tacrolimus in children with glomerular disease require further studies because of the few studies to date.

Given that children with nephrotic syndrome during relapse have low levels of serum albumin, the pharmacokinetics of tacrolimus may be influenced by the nephrotic state. However, one study reported that the pharmacokinetic profiles of tacrolimus were consistent in the remission and relapse stages of nephrotic syndrome in children.[130]

Therapeutic drug monitoring (TDM) is still needed to adjust the dose of the drug after the use of tacrolimus. Pharmacogenetic testing and trough concentration-based TDM complement each other. Based on clinical practice in kidney transplant patients, a pharmacogenetic-based personalized dose of tacrolimus can reduce the number of TDM and time to achieve the target trough concentrations.

At present, there is no TDM-based randomized controlled trial (RCT) in children with glomerular diseases to evaluate optimal target level. The current target concentrations are based on observational trials. As shown in Table 1, the target C_0 of tacrolimus was set at 5-10 ng/mL in four clinical trials. The pharmacokinetic/pharmacodynamic (PK/PD) analysis and TDM-based RCT trials are still lacking. The optimal dose and target concentrations of tacrolimus in children with glomerular disease are still needed to evaluate in further studies.

Nephrotoxicity is the main side effect of tacrolimus. Tacrolimus can activate the major vasoconstriction systems, such as the renin-angiotensin and endothelin systems, and increase the activity of the sympathetic nerve. On the other hand, tacrolimus can inhibit the synthesis of nitric oxide (NO) and NO-mediated vasodilation, and increase the formation of free radicals. Altogether, these processes can lead to endothelial dysfunction and contribute to the impairment of organ function, including kidney.[131]

The early nephrotoxicity of tacrolimus is related to irrational drug use, especially when the dosage is too high or the plasma concentration is high. Undre et al believe that the risk of renal toxicity is greatly increased when the trough whole blood concentration of tacrolimus is greater than 20 ng/mL.[132] High tacrolimus levels are related to acute nephrotoxicity, but the relationship with chronic toxicity is less clear. Furthermore, some pharmacodynamic genes (TGF-β, CYP2C8, ACE, CCR5) may impact recipients' risk of developing tacrolimus-induced nephrotoxicity.[133]

3 | CONCLUSION

There is growing evidence that tacrolimus is a promising agent for induction therapy in children with glomerular disease. More prospective controlled trials with long follow-up are needed to definitely prove the effectiveness, safety and pharmacokinetics of tacrolimus in children with glomerular disease.

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY[132] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20. [133]

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COMPETING INTERESTS

The authors have no competing interest to declare.

CONTRIBUTORS

G.X.H and L.L.S retrieved data, carried out the initial analyses and drafted the initial manuscript. L.Q.S and D.F.Z gave advice on the project and manuscript. E.J.A and W.Z conceptualized, designed and initiated the study. All the authors contributed to writing the manuscript and approved the final manuscript as submitted.

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