Expert consensus on long-term management of immunosuppressants in Chinese renal transplant recipients

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Abstract

Renal transplantation has significantly improved the quality of life of patients with end-stage renal disease. Optimal balance between insufficient and excessive immunosuppression of immunosuppressive therapy after transplantation is essential to improve patients' survival. The GuangDong Pharmaceutical Association in China has developed an expert consensus on the long-term management of immunosuppressants in Chinese renal transplant recipients. Emphasis is placed on the drug regimen of the long-term immunosuppressive maintenance therapy after transplantation, the drug-drug interactions of immunosuppresants, and the chronic disease management of renal transplant recipients.

Renal transplantation is the most ideal treatment for end-stage renal failure, and immunosuppressants are required for long-term prevention of allograft rejection after surgery. Immunosuppressive therapy has narrow therapeutic index and large inter-individual differences. Insufficient or excessive immunosuppression can affect patients' quality of life. Therefore, the appropriate selection and use of immunosuppressants after transplantation is critical for physicians and clinical pharmacists. Long-term management of immunosuppressants is mainly through hospital outpatient clinics, and the establishment of a doctor-pharmacist joint renal transplant outpatient clinic has great significance for increasing patients' survival rate and quality of life. The purpose of this consensus is to provide guidance for the long-term management of immunosuppressive therapy in adult renal transplantation, improving treatment safety and effectiveness for patients.

1 Long-term immunosuppressive maintenance therapy regimen after renal transplantation

Immunosuppressive regimens for renal transplantation mainly include perioperative immune induction regimens and long-term immunosuppressive maintenance therapy regimens after transplantation. The latter is mostly a combination of different types of oral immunosuppresants, which is used to effectively inhibit the specific activation of lymphocytes against the graft antigens, thus avoiding the occurrence of rejection as much as possible.

1.1 Immunosuppressive maintenance therapy

Immunosuppresants commonly used (Table 1) include calcineurin inhibitors (CNIs) such as tacrolimus (Tac) and cyclosporine A (CsA); mycophenolic acid (MPA) drugs such as mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), in which MPA is the active product of MMF and EC-MPS; glucocorticoids such as prednisone and methylprednisolone. Other medications include sirolimus (SRL), azathioprine, mizoribine and leflunomide.

Table 1 Drugs for immunosuppressive maintenance therapy in renal transplantation

Classification	Drug name	Initial dosing regimen[1-2]	Basis for dosing adjustment*
CNI	CsA	3-6 mg/kg/d in 2 divided doses	The dose can be adjusted according to drug concentration. Targeted ranges of trough concentration are 150-300 ng/mL in the first month post-transplantation, 150-250 ng/mL in 1-3rd month post-transplantation, 120-250 ng/mL in 4-12th month post-transplantation, and 80-120 ng/mL in more than 1 year post-transplantation [2].
	Tac	0.05-0.15 mg/kg/d in 2 divided doses (once daily for extended release capsules)	The dose can be adjusted according to drug concentration. Targeted ranges of trough concentration are 8-12 ng/mL in the first month post-transplantation, 6-10 ng/mL in 1-3rd month post-transplantation, 4-10 ng/mL in 4-12 month post-transplantation, and 4-8 ng/mL in more than 1 year post-transplantation [2]. For denovo anti-donor specific antibody positive renal transplant recipients with stable renal function, maintenance of trough concentrations greater than 6 ng/mL is recommended. The initial dose can be adjusted according to the cytochrome P450 (CYP) 3A5 genotype of patients [3]: standard dose for slow metabolizer (*CYP3A5*3/*3*); 1.5-2 times of the standard dose for rapid metabolizer (*CYP3A5*1/*1* or *CYP3A5*1/*3*) but the daily dose should not higher than 0.3 mg/kg.

Antimetabolic drugs	MMF	0.75-1.0 g twice daily	The dose can be adjusted according to MPA concentration. The effective therapeutic AUC (determined by the HPLC method) range of MPA [4-6] is 30-60 (mg·h)/L. The values measured by the enzyme-multiplied immunoassay technique (EMIT) are higher than that measured by the HPLC method, so the targeted range of AUC increases accordingly.
	EC-MPS	360-720 mg twice daily	The dose can be adjusted according to MPA concentration. The effective therapeutic AUC (determined by the HPLC method) range of MPA [4-6] is 30-60 (mg·h)/L. The values measured by the EMIT are higher than that measured by the HPLC method, so the targeted range of AUC increases accordingly.
	Azathioprine	1-2 mg/kg once daily	The dose can be adjusted according to the patient tolerance.
	Mizoribine	2-3 mg/kg/d, taking a dose all at once in the morning or in 2 divided doses; gradually reducing to 1-3 mg/kg/d for maintenance treatment.	The dose can be adjusted according to drug concentration. Targeted range of trough concentration[7]: 1-3 mg/L.

	Leflunomide	When BK virus infection or BK virus nephropathy is confirmed, leflunomide can be used for maintenance therapy, with a loading dose of 50 mg once daily for the first 3 to 5 days, followed by 20 mg once daily.	The dose can be adjusted according to the patient tolerance.
Mammalian sirolimus target protein inhibitor	SRL	Loading dose of 6 mg once daily for the first day, followed by 2 mg once daily.	The dose can be adjusted according to drug concentration. Targeted range of trough concentration[2,8-9]: 4-8 μg/L.
Glucocorticoid	Prednisone	Starting at 10-60 mg/d, gradually decreasing to 10-15 mg/d by day 30 post-transplantation, 10 mg/d in 2-3rd month post-transplantation, and adjusting to 5.0-7.5 mg/d or a lower dose for maintenance therapy after half a year.	The dose can be adjusted according to the patient tolerance.

*All drug concentrations are steady-state concentrations. CNI, calcineurin inhibitor; CsA, cyclosporine A; Tac, tacrolimus; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; SRL, sirolimus; AUC, area under the concentration-time curve; HPLC, high-performance liquid chromatography; MPA, mycophenolic acid.

1.2 Blood concentration monitoring of immunosuppresants

1.2.1 CsA

The peak concentration (C_2) or trough concentration (C_0) of CsA in blood can be monitored after transplantation. Targeted ranges of C_0 and C_2 are 150-300 ng/mL and 1000-1500 ng/mL within the first month post-transplantation, 150-250 ng/mL and 800-1200 ng/mL in the 1-3rd month post-transplantation, 120-250 ng/mL and 600-1000 ng/mL in the 4-12th month post-transplantation, and 80-120 ng/mL and >400 ng/mL in more than 1 year post-transplantation, respectively[2]. For initial treatment at the early postoperative stage, CsA concentrations can be monitored every other day until the targeted range is reached. In addition, CsA concentrations should be measured when patients exhibit decreased renal function that indicates possible rejection or CsA related nephrotoxicity, or when CsA concentrations may be altered.

1.2.2 Tac

The blood trough concentration of Tac can be monitored after transplantation and the monitoring frequency is the same as CsA. Targeted ranges of trough concentrations are 8-12 ng/mL within the first month post-transplantation, 6-10 ng/mL in the 1-3rd month post-transplantation, 4-10 ng/mL in the 4-12th month post-transplantation, and 4-8 ng/mL in more than 1 year post-transplantation [2].

1.2.3 MPA

The area under the concentration-time curve (AUC) of MPA can be monitored after transplantation. The AUC of MMF can be calculated by the 4-point method of blood concentration at 0.5 h ($C_{0.5}$), 1.5 h ($C_{1.5}$), 4 h (C_4), and 9 h (C_9), or by the 10-point method at 0 h (C_0), 0.5 h ($C_{0.5}$), 1 h (C_1), 1.5 h ($C_{1.5}$), 2 h (C_2), 3 h (C_3), 4 h (C_4), 6 h (C_6), 9 h (C_9), and 12 h (C_{12}); the AUC of EC-MPS can be calculated by the blood concentration at 0 h (C_0), 1 h (C_1), 2.5 h ($C_{2.5}$), 4 h (C_4), 5 h (C_5), 6 h (C_6), 7 h (C_7), 8 h (C_8), 9 h (C_9), 10 h (C_{10}), and 12 h (C_{12}). The effective therapeutic range of AUC determined by HPLC method is 30-60 (mg·h)/L[2,4-6]. It is recommended to monitor the AUC of MPA in the early stage after transplantation and if adverse drug reactions occur.

1.2.4 SRL

The target trough concentration in blood of SRL is 4-8 μg/L post-transplantation[2,8,9]. The trough concentration can be monitored after 3 to 4 days of the loading dose; when the dose is adjusted, concentration monitoring should be performed after the new maintenance dose is continuously used for 7-14 days[10].

1.3 Immunosuppressive combination regimen

There are variety of combination therapy regimens to maintain immunosuppression, which can enhance the effect and lower the dose of a single drug, thus reducing the incidence of drug adverse effects. Tac has a stronger immunosuppressive effect and a lower incidence of adverse reactions than CsA and become the first choice of CNI drugs post-transplantation. The main regimen of post-transplant immunosuppressive maintenance therapy is a CNI (Tac or CsA) based triple regimen that combined with antimetabolic drugs (such as MPA or mizoribine) and glucocorticoids. The choice of maintenance regimen should follow scientific, individual and rationalized dosing principles because of the differences in the mechanism of action, intensity of immunosuppression and adverse effects of different immunosuppresants.

1.3.1 CNI-based triple immunosuppressive regimen

"Tac + MPA + glucocorticoids" was recommended as the standard immunosuppressive regimen after renal transplantation by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines and the U.S. Food and Drug Administration (FDA), and it was also adopted by the Chinese guidelines and various transplant centers in China.

(1) Tac is usually initiated right after surgery and its blood concentrations (C_0) should be measured on day 3 of therapy. The dose should be adjusted in time if necessary to attain the C_0 target within 1 week post-transplantation. Testing the patient's *CYP3A5* genotype before transplantation will help to determine the initial dose of Tac. Mutations at the CYP3A5*3 (rs776746) locus will slow down the metabolism of Tac in vivo, so a standard dose is sufficient for slow metabolizers; rapid metabolizers should take 1.5 to 2.0 times of the standard dose, but the daily dose should not higher than 0.3 mg/kg. Long-term maintenance dose should be adjusted based on the target blood concentrations, in small amounts, to avoid large fluctuations.

(2) In the long-term maintenance phase, the dose of MPA drugs should be appropriate, meaning within the patient's tolerance range and without causing bone marrow suppression. The dose of MPA drugs should take into account the patient's gender, body weight, test indicators (e.g., blood leukocyte count) and tolerance to the drug. The overall tolerance to MPA drugs of Chinese is lower than that of European and American whites.

(3) Glucocorticoids are necessary for the prevention of acute T-cell-mediated rejection. The routine use of glucocorticoids follows the principle of decreasing doses, with prednisone, for example, starting at 30 mg/d and decreasing gradually to 5.0-7.5 mg/d or lower for maintenance therapy.

(4) For low-risk individuals who taken the CNI-based immunosuppressive regimen for a long time and have not experienced rejection, the maintenance treatment can be switch to a CNI-free immunosuppressive regimen if they develop a chronic increase in serum creatinine that is confirmed to be related to the CNI nephrotoxicity. The use of CNI-free immunosuppressive regimens is currently controversial, and is not recommended, particularly for initial use after renal transplantation, which requires close attention to safety and tolerability issues.

(5) To avoid nephrotoxicity induced by CNI in the elderly patients, patients with delayed recovery of transplanted kidney function or general donor kidney quality are usually sensitive to CNI nephrotoxicity, an immunosuppressive regimen of low CNI combined with adequate/enhanced MPA can be used.

1.3.2 Reduction of CNI immunosuppression maintenance dose

Reducing CNI dose rather than completely withdrawing may be a better option, because of the dose-dependent nephrotoxicity of CNI. Currently, there are two alternative regimens for the dose reducing: low-dose CNI + SRL + MPA + glucocorticoids, or low-dose CNI + MPA + glucocorticoids[2].

1.3.2.1 Low-dose CNI + SRL + MPA + glucocorticoids

(1) CNI effects in the early phase of the T cell cycle (G0 to G1 phase), while SRL acts as a blocker in the G1 to S phase of the T cell proliferative cycle. As CNI and SRL influence T cell activation at different stages, the combination of these two has a synergistic immunosuppressive effect.

(2) SRL has little nephrotoxicity and has unique immunological advantage with induced tolerance. The toxic

effects of CNI are dose-dependent, so reducing the dose can significantly reduce its nephrotoxicity.

(3) When combined with CNI, the trough concentration of SRL need not be too high. The sum of Tac + SRL blood concentration at 8-12 ng/mL is sufficient, and also helpful to reduce the adverse effects of SRL.

1.3.2.2 Low-dose CNI + MPA + glucocorticoids

Although the patient can tolerate a full dose of MPA, the dose of CNI should not be reduced too much (generally by 30% or less), because the overall immunosuppressive strength of MPA might be lower than SRL. Considering the risk of rejection, it is recommended to use only for long-term stable patients who are at low immune risk.

1.3.3 CNI drug-to-drug interconversion regimens

CNI drugs mainly include CsA and Tac, and renal transplant recipients have different tolerance to the two drugs. Switching between CNI drugs is generally considered when patients do not tolerate the drugs used or obvious adverse reactions occur[2].

(1) Tac is recommended in priority, but CsA is often chosen for patients with high body mass index (BMI), diabetes, or abnormal islet function.

(2) CsA can be converted to Tac at a dose of 30-50 mg:1 mg, with 50 mg:1 mg usually recommended, in case of the occurrence of the adverse effects such as the increase of serum creatinine due to insufficient immunity after the use of CsA, hirsutism, and gingival hyperplasia. When the two drugs are switched, the converted CNI should be taken after the former CNI is stopped for 1 time (12 h); then, the blood concentration should be retested 3-7 days after the switch to reach the target concentration of converted CNI as soon as possible. The first dose of Tac should be given 12 h after the last administration of CsA. If the blood C_0 of CsA is >300 ng/mL, the administration of Tac should be delayed until the C_0 of CsA is <300 ng/mL [2].

(3) Tac can be converted to CsA when the blood concentration is too low after the use of Tac or the dose is too large, or when the adverse reactions such as drug-related kidney injury or drug-related diabetes occur. The regimen and the timing for converting Tac to CsA is the same as those for converting CsA to Tac described above[2].

1.3.4 MPA drug conversion regimens

When patients develop MPA-related gastrointestinal symptoms (severe diarrhea, bloating, etc.), bone marrow suppression, active HCV replication, CMV or BK virus infection, etc., the MPA can be reduced or discontinued Switching MAP to the second-line antimetabolic drugs (e.g., mizoribine) is another option.

2 Drug interactions of immunosuppressants

Renal transplant patients administered with immunosuppressant therapy may encounter complications or adverse drug reactions such as bacterial or fungal infections, hypertension, hyperglycemia or dyslipidemia, thus requiring multidrug regimens. In addition, health supplements, herbs and foods taken by transplant patients may interact with immunosuppressants, and affect drug_efficacy or concentrations resulting in adverse effects.

Drug interactions can be mechanistically classified into pharmacological, pharmacokinetic and

pharmacodynamic interactions, among which interactions caused by induction and inhibition of cytochrome P450 (CYP) are the most common. Inhibitors and inducers of CYP3A4/5 and P-glycoprotein(P-gp) may affect the blood concentrations of Tac, CsA and SRL, because these drugs are metabolized by CYP3A4 or transported by P-gp. CsA is an inhibitor of CYP3A4 and P-gp, so it may increase concentrations of other drugs that are metabolized by CYP3A4 or transported by P-gp. MPA drugs have hepatoenteric circulation and compete with other drugs that is actively secreted by renal tubular, which have potential drug interactions as well. The US UpToDate database classifies the strength of drug interactions into Class A (drug interactions unknown), B (no need to adjust therapeutic regimen), C (increase monitoring frequency), D (consider adjusting therapeutic regimen), and X (avoid combination). This consensus focuses on clinically significant drug interactions at Class C, D, and X.

2.1 CsA

2.1.1 Common drugs that increase blood concentration of CsA

(1) Some macrolide antibiotics [such as clarithromycin (Class D), erythromycin (Class C), and azithromycin (Class C)]: clarithromycin and erythromycin can increase the blood concentration of CsA by inhibiting CYP3A4. The American Society for Transplantation recommends avoiding the combination of CsA with clarithromycin or erythromycin as far as possible. The dose of CsA should be reduced by half if the combination needed[11]. Azithromycin may increase the blood concentration of CsA by inhibiting P-gp and affecting biliary excretion [12].

(2) Some calcium channel blockers (Class C, such as diltiazem, nicardipine, and verapamil): it can increase the blood concentration of CsA by inhibiting CYP3A4[13 -14] .

(3) Chloramphenicol (Class D): it can increase the blood concentration of CsA by inhibiting CYP3A4. The American Society for Transplantation recommends 25% reduction in CsA dose when used in combination[11].

(4) Wuzhi capsules and Wuzhi tablets (Class C): it can increase the blood concentration of CsA by inhibiting CYP3A. The effect is more pronounced in fast metabolic carriers of CYP3A5[15].

(5) Metoclopramide (Class C): CsA is more rapidly transported to the small intestine for absorption by promoting gastrointestinal motility, reducing its chance of degradation by other metabolic mechanisms[16].

(6) Amiodarone (Class C): it can increase the blood concentration of CsA by inhibiting CYP3A4 and P-gp[17].

(7) Propafenone (Class C): it can increase the blood concentration of CsA by inhibiting P-gp[18].

(8) Antifungal drugs (such as voriconazole (Class D)[19], itraconazole (Class D)[20], posaconazole (Class D)[21] and ketoconazole (Class D)[22], fluconazole (Class C)[23] , etc.) inhibit CYP3A, and cause interactions between antifungal drugs and immunosuppressants, which are shown in Table 2. The combination of CsA and voriconazole may result in 70% increase in AUC of CsA, and it is recommended that the dose of CsA should be halved and the blood concentration of CsA should be monitored when used in combination with voriconazole. The dose of CsA should be reduced by 50% when used in combination with ketoconazole or itraconazole, by 25% when combination with posaconazole, and also should be reduced when used in combination with other azoles.

Table 2 Interactions of antifungal drugs and immunosuppressants

Antifungal drugs	Affected immunosuppressants		
	CsA	Tac	SRL
Fluconazole	Increases CsA concentration	Up to 5-fold increase of Tac (oral) concentration and no significant change of Tac (intravenous)[24]	Increases SRL concentration
Itraconazole	Increases CsA concentration, which recommends reduction of CsA dose in half	Increases Tac concentration	Increases SRL concentration
Voriconazole	70% increase in AUC with CsA, which recommends reduction of CsA dose in half	2-fold increase in C_{max} and 3-fold increase in AUC with Tac, which recommends two-third reduction in Tac dose	6.6-fold increase in C_{max} and 11-fold increase in AUC with SRL, which avoid combination
Posaconazole	Increases CsA concentration, which recommends 25% reduction in CsA dose	121% increase in C_{max} and 358% increase in AUC with Tac, which recommends two-third reduction in Tac dose	6.7-fold increase in Cmax and 8.9-fold increase in AUC, which recommends nine-tenth reduction in SRL dose

2.1.2 Common drugs that reduce the blood concentration of CsA

Some drugs reduce CsA concentration by induction of CYP3A4, such as anti-tuberculosis drugs: rifampicin (Class D)[25], rifabutin (Class C)[26], phenobarbital (Class D)[27], carbamazepine (Class D)[28], phenytoin sodium (Class D)[29], methylprednisolone (Class C)[30], prednisone (Class C)[31] and prednisolone (Class C)[32], etc. Some drugs reduce CsA concentration by interfering with its absorption, such as octreotide (Class C)[33] and so on.

2.1.3 Common drugs affected by CsA

(1) CsA inhibits CYP3A4, P-gp, and organic anion transporting polypeptide 1B1(OATP1B1), and therefore it should be avoided in combination with statins (such as atorvastatin (Class X)[34], simvastatin (Class X)[35], and lovastatin (Class X) [36]) that are primarily metabolized by CYP3A4 , because of increasing risk of rhabdomyolysis. The risk of muscle injury is reduced but still exists when it combined with statins (such as rosuvastatin (Class D)[37], fluvastatin (Class D)[38], and pravastatin (Class D)[39]) that are not metabolized by CYP3A4 but are transported by OATP1B1, so it should be routinely monitored or replaced with other lipid-lowering agent. Specifically, the starting dose of pravastatin is 10 mg per day and the maximum dose of pravastatin is limited to 20 mg per day when it combined with CsA, and at the same time monitoring the myotoxicity of pravastatin. The daily dose of rosuvastatin is limited to 5 mg while monitoring the toxicity of rosuvastatin, when it combined with CsA.

(2) The combination of CsA and Tac (Class X) increases the blood concentration of Tac because of their largely identical metabolic pathways and high plasma protein binding. Meanwhile, Tac may also result in increasing blood concentration of CsA. Therefore, the combination of Tac and CsA is not recommended. Pay attention to patients treated with Tac when they previously treated with CsA[40].

(3) The combination of CsA and dabigatran etexilate (Class C)[41] increases the concentration of dabigatran etexilate by inhibiting P-gp, which may increase the risk of bleeding. It should be avoided to combine CsA and dabigatran etexilate in cases of poor renal function.

(4) The combination of CsA and SRL (Class D)[42] increases the concentration of SRL by inhibiting CYP3A4 and P-gp, which required to closely monitor the concentration of SRL. It is recommended to take SRL orally 4h after the administration of CsA.

(5) The combination of CsA and repaglinide (Class D)[43] increases the concentration of repaglinide and the risk of hypoglycemia by inhibiting CYP3A4. It is required to monitor the blood glucose levels and limit daily dose of repaglinide to no more than 6 mg.

(6) The combination of CsA and colchicine (Class D)[44] increases the concentration of colchicine by inhibiting P-gp. It aiso increases some tissues distribution (e.g., brain) of colchicine, which resulted in increasing toxicity (myopathy, neurotoxicity).

(7) The combination of CsA and digoxin (Class C)[45] increases the concentration of digoxin by inhibiting P-gp, which may result in severe digitalis toxicity. It is required to monitor the blood concentration and toxic reactions of digoxin.

(8) CsA reduces the metabolism of etoposide (Class D) by inhibiting CYP3A4 and P-gp[46]. 50% dose reduction of etoposide may be considered if the patient is receiving or has recently received therapy of CsA .

(9) It should be avoided to combined CsA and doxorubicin (level X) , because CsA inhibits CYP3A4 and P-gp[47].

2.1.4 Common drugs that affect the efficacy in combination with CsA

(1) Aminoglycosides (Class C)[11], amphotericin B (Class C)[48] may enhance the nephrotoxicity of CsA (mechanism of interaction is unknown, maybe cause by synergistic or additive effects of nephrotoxicity).

(2) Angiotensin II receptor antagonists (Class C)[49] with potassium-preserving effects may enhance the potassium-raising effect of CsA.

(3) CsA may increase the toxicity and blood concentration levels of caspofungin (Class D)[50]. Caspofungin may also increase the blood concentration of CsA. It should be weighed against between the potential benefits of caspofungin and the possible increased risk of hepatotoxicity. Liver function also should be monitored during combination (mechanism of interaction is unknown).

(4) Some non-steroidal anti-inflammatory drugs (NSAIDs) (Class D)[51] may increase the blood concentration and nephrotoxicity of CsA. CsA may also increase the blood concentration of NSAIDs (mechanism of interaction is unknown; disruption of prostaglandin synthesis by NSAIDs may predispose nephrotoxicity of CsA even if its concentration is not elevated; CsA may affect metabolism of diclofenac, especially its first-pass metabolism by inhibiting CYP3A4/2C9). Drug interactions of CsA are shown in Table 3.

Table 3 Drug interactions of CsA

Type of Drug Interaction	Interaction Strength*	Co- administered drugs
Increase CsA concentration	Class D	Clarithromycin, chloramphenicol, voriconazole, itraconazole, posaconazole, ketoconazole
	Class C	Pentaerythritol, azithromycin, erythromycin, diltiazem,nicardipine, verapamil, metoclopramide, amiodarone, propafenone, fluconazole
Reduce CsA concentration	Class D	Rifampicin, phenobarbital, carbamazepine, phenytoin sodium
	Class C	Rifabutin, methylprednisolone, prednisone, prednisolone, oxytetracycline
	Class X	Atorvastatin, simvastatin, lovastatin,

		doxorubicin, Tac
Concentration affected by CsA	Class D	Rosuvastatin, fluvastatin, pravastatin, SRL, reserpine, glibenclamide, colchicine, etoposide
	Class C	Dabigatran etexilate, digoxin
Efficacy affected by CsA	Class D	Caspofungin, some NSAIDs
	Class C	Aminoglycosides, amphotericin B, angiotensin II receptor antagonists

Note:* Interaction strength levels refer to the UpToDate systematic classification.

2.2 Tac

Drugs that induce or inhibit CYP3A4/5 can have an effect on the metabolism of Tac, which is mainly metabolized by CYP3A. Drugs that are known to increase or reduce blood levels of Tac are similar to those affecting CsA concentration. The common drug interactions of Tac are shown in Table 4.

2.2.1 Common drugs that increase blood levels of Tac

(1) Antifungal drugs [such as voriconazole (Class D)[52], itraconazole (Class D)[53], clotrimazole (Class C)[54], posaconazole (Class D)[21], ketoconazole (Class D)[55], and fluconazole (Class D)[56], etc.]. Common drug interactions between this class of drugs and immunosuppressants are shown in Table 2. Inhibition of CYP3A by imidazole antifungals reduce the metabolism of Tac and can significantly increase Tac concentration and nephrotoxicity. Blood concentration of Tac and creatinine clearance levels need to be monitored daily if imidazole antifungals must be co-administered with Tac. Dose reduction of Tac by 50% on day 1, 70% on day 3, and 75% on day 14 may be considered when fluconazole or itraconazole therapy initiated. The intensity of itraconazole-Tac interaction is greater in elderly patients and in patients carrying CYP3A5*3 allele. Tac C_{max} increases 2-fold and AUC increases 3-fold when Tac is combined with voriconazole. It is recommended to reduce Tac dose by two-third and monitor the blood concentration of voriconazole and Tac during the 1st to 3rd days of co-administration. Besides, blood concentration of Tac should be monitored constantly after voriconazole discontinuation and dose should be adjusted. In addition, Tac dose should also be reduced by two-third if combine with posaconazole. When co-administered with ketoconazole, dose of Tac may need to be adjusted and it is recommended that dose of Tac be empirically reduced by half.

(2) Some macrolide antibiotics [e.g., clarithromycin (Class D)[11], erythromycin (Class C)[57], and azithromycin (Class C)[58], etc.]. Macrolide antibiotics of the fourteen-membered ring could form inactive complexes with CYP3A isozymes, which inhibit the metabolism of Tac in the liver and small intestine and then increase the blood concentration of Tac. Moreover, the interaction of these two classes of drugs can cause acute renal impairment. Azithromycin, which does not induce or inhibit the CYP450 system, is relatively safe. But it has an inhibitory effect on P-gp, so blood concentration of Tac and renal function also

should be monitored closely when the two drugs are combined.

(3) Some calcium channel blockers (Class C, such as diltiazem, nicardipine, and verapamil[59]). Dihydropyridine calcium antagonists are strong inhibitors of the CYP3A isoenzyme, which can increase blood concentration of Tac by inhibiting its metabolism in the liver to slow its elimination.

(4) Chloramphenicol (Class D)[60] slowed down the elimination of Tac by inhibiting CYP3A and increased the blood concentration of Tac by prolonging its half-life.

(5) Protease inhibitors can inhibit drugs metabolism by CYP3A. Therefore, combination of ritonavir (Class D)[61] and Tac should be avoided, and the dose of Tac may need to be reduced if the combination of ritonavir is required. At the same time, the Tac concentration should be monitored closely to determine its dose. Zidovudine and lamivudine are safe relatively, but routinely monitoring blood concentration of Tac and renal function is still required.

(6) Reproductive and endocrine system modulators. Estrogen derivatives (Class C)[62] such as diethylstilbestrol have an inhibitory effect on the metabolism of Tac, which can increase Tac concentration (mechanism of interaction is still unknown).

(7) Wuzhi capsules and Wuzhi tablets (Class C)[63-65] can increase blood concentration of Tac by inhibition of CYP3A. This effect is more significant in fast metabolic type carriers of CYP3A5. When the patient is CYP3A5 fast metabolizer, the combination of Wuzhi capsules or Wuzhi tablets can increase the blood concentration of Tac by one-fold.

(8) Proton pump inhibitors (Class C)[66] such as lansoprazole can inhibit CYP3A4-mediated metabolism of Tac, resulting in increased blood concentration.

(9) Levofloxacin (Class C)[67] increases Tac blood concentration and enhances the effect of Tac in prolonging Q-T interval.

(10) Metoclopramide (Class C)[68] (increases Tac absorption by promoting gastric emptying) and tigecycline (Class C)[69] (mechanism of interaction is unknown) can also increase the blood concentration of Tac.

2.2.2 Common drugs that lower blood levels of Tac

(1) Anti-tuberculosis drugs [such as rifampicin (Class D)[70], rifapentine (Class C)[71], rifabutin (Class C)[72], etc.]. Rifampin is a strong inducer of CYP3A4 and P-gp, which can induce the metabolism of Tac by hepatic and intestinal CYP3A enzyme system and P-gp, significantly increase the elimination, reduce the bioavailability, and decrease the blood concentration of Tac. Rifabutin also decreases blood concentration of Tac, but the induction effect is weaker than that of Rifampicin. Tac blood concentration should be closely monitored when rifampin or rifabutin was used in combination with Tac.

(2) Phenobarbital (Class D)[73], carbamazepine (Class D)[74], phenytoin sodium (Class D)[75], and nafcillin sodium (Class C) [76] can affect blood concentration of Tac by inducing CYP3A4.

2.2.3 Effect of Tac on the metabolism of other common drugs

(1) When Tac is combined with CsA (Class X), the half-life of CsA may be prolonged due to their largely identical metabolic pathways and high plasma protein binding, resulting in increased blood concentration of

CsA. In addition, nephrotoxicity may increase due to synergistic effects. At the same time, CsA may also increase Tac concentration and its nephrotoxicity. Therefore, the combination of Tac and CsA is not recommended, and care should be taken when Tac is given to patients previously treated with CsA[40].

(2) The combination of Tac and colchicine (Class C)[77 -78] increases colchicine concentration and its toxicity (myopathy and neurotoxicity), requiring a reduction in the dose of colchicine (the mechanism of interaction is unknown and may be related to the inhibiting effect of Tac on CYP3A4 or P-gp).

(3) Tac decreases clearance of estrogen derivatives (Class C)[62], leading to increased exposure of hormone. Therefore, it is required to special care in the choice of contraception (mechanism of interaction is unknown).

2.2.4 Common drugs that affect the efficacy in combination with Tac

(1) Aminoglycosides (Class C)[11] (synergistic or additive effects of nephrotoxicity), NSAIDs (Class C)[79] (mechanism of interaction is unknown) may enhance the nephrotoxicity of Tac.

(2) Amiodarone (Class C)[80-81]: Tac enhances the effect of amiodarone in prolonging Q-T interval. And then amiodarone can prolong Q-T interval by inhibiting P-gp and CYP3A4 to increase blood concentration of Tac.

Table 4 Drug interactions of Tac

Type of Drug Interaction	Interaction Strength*	Co- administered drugs
Increase Tac concentration	Class D	Voriconazole, itraconazole, posaconazole, ketoconazole, fluconazole, clarithromycin, chloramphenicol, ritonavir
	Class C	Wuzhi preparation, clotrimazole, erythromycin, azithromycin, diltiazem, verapamil, estrogen derivatives, proton pump inhibitors, levofloxacin, metoclopramide, tigecycline
Reduce Tac concentration	Class D	Rifampicin, phenobarbital, carbamazepine, phenytoin sodium
	Class C	Rifabutin, rifapentine, nafcillin sodium
Concentration affected by Tac	Class X	CsA
	Class C	Colchicine, estrogen derivatives
Efficacy affected by Tac	Class C	Aminoglycosides, some NSAIDs, amiodarone

Note: * Interaction strength levels refer to the UpToDate systematic classification.

2.3 Mycophenolic acid derivatives

(1) When MPA is combined with drugs that interfere with the enterohepatic circulation, the latter decreases the efficacy of MPA.

(2) MPA, when combined with acyclovir (Class C)[82] or ganciclovir (Class C)[83], both competitively excreted through the renal tubules, leading to increasing blood concentration of antivirals and increasing risk of adverse drug reactions.

(3) Magnesium hydroxide (Class D), aluminum hydroxide (Class D)[84] may reduce the absorption of MPA when combined with MPA due to antacid effect or chelation. So the combination of EC-MPS is not recommended, while if combined with MMF. it is recommended to take aluminum hydroxide at least 2 h after the administration of MMF.

(4) MPA does not affect the pharmacokinetics of CsA, but CsA (Class D)[85] affects the hepatic and intestinal circulation and can decrease blood concentration of MPA.

(5) Proton pump inhibitors (Class C)[86] may reduce blood concentrations of MMF when used in combination with MMF due to interference with absorption of MPA and/or hydrolysis due to elevated gastric pH, whereas EC-MPS are not affected by this, making EC-MPS more advantageous when using proton pump inhibitors.

(6) Rifampicin (Class D)[87] may reduce blood concentration of MPA by induction of CYP3A4 when combined with MPA.

2.4 Immunosuppressants-vaccine interactions

2.4.1 Inactivated vaccine (Class D)

Immunosuppressants may diminish the therapeutic effect of inactivated vaccines, so inactivated vaccines should be administered at least 2 weeks prior to initiation of immunosuppressants if possible. Patients who received vaccine less than 14 days before or during treatment should be revaccinated at least 2 to 3 months after the end of treatment.

2.4.1.1 Rabies vaccine (Class D)

Immunosuppressants may reduce the therapeutic effect of rabies vaccine and rabies vaccination can be completed at least 2 weeks prior to initiation of immunosuppressive therapy. If post-exposure rabies vaccination is required during immunosuppressive therapy, the 5th dose of vaccine should be administered and check for rabies antibodies is required[88].

2.4.1.2 Influenza virus vaccine (Class D)

Immunosuppressants may reduce the therapeutic effect of influenza virus vaccines. Influenza vaccination can be given at least 2 weeks before starting immunosuppressive therapy. If vaccination occurs before or less than 2 weeks after immunosuppressive therapy, the vaccine can be revaccinated 2 to 3 months after treatment stopped[89-90] if immunity is restored.

2.4.2 Live attenuated vaccine (Class X)

Live attenuated vaccine may enhance the toxic effects of immunosuppressants (risk of vaccine-associated infections) and weaken the therapeutic effects of immunosuppressants, (e.g., rubella vaccine, varicella vaccine, dengue vaccine, polio vaccine, etc.). In addition, immunosuppressants may weaken the therapeutic effects and enhance the toxic effects of the live rubella or varicella vaccines[91].

3 Chronic disease management in renal transplant patients taking immunosuppressants

The management of patients after transplantation is of great importance. Regular follow-up, individualized medication guidance, and health education for transplant recipients are important to improve patients' quality of life and long-term survival of allograft kidneys. The methods of chronic disease management can be outpatient follow-up, telephone follow-up and internet follow-up. Physicians and pharmacists can form a management team, with physicians focusing on disease assessment, management of complications and treatment planning, and pharmacists focusing on managing recipient's medication, timely adjustment of medication doses, timely detection of adverse reactions and potential interactions and improvement of patient compliance.

3.1 Management style

Management of renal transplant patients usually starts from the time patients are discharged from the hospital, and the methods mainly include physician or pharmacist outpatient clinic or joint clinic, telephone or SMS follow-up, WeChat or QQ follow-up, mobile application (APP) follow-up, and home follow-up.

3.1.1 Physician or pharmacist outpatient clinic or joint clinic

Outpatient clinic management is the most common type of management, where patients can visit a physician or pharmacist clinic for regular post-operative treatment review, and physicians or pharmacists can provide guidance on medication and suggest precautions.

3.1.2 Telephone follow-up management

Telephone follow-up visits can be made to understand the recipients' medication status and recorded in the follow-up file. Reminding and supervising the patients with poor compliance to take their medication on time or to follow up on time should be focused on, and giving them health education and guidance.

3.1.3 Network follow-up management

The follow-up work can be carried out by establishing relevant websites or through WeChat official account and APP, which can greatly simplify the follow-up process to improve work efficiency and facilitate the preservation of follow-up data to reduce economic costs.

3.1.4 Other management methods

For special types of recipients, such as post-operative patients with limited mobility or language communication difficulties, a home follow-up management model can be adopted. During the COVID-19 epidemic, patients need to be managed online through the internet, telephone, WeChat or mobile APP.

3.2 Management Content

An important guarantee for long-term survival of the allograft kidneys is the strict implementation of a standardized follow-up plan, with the number and frequency of follow-up visits depending on the length of postoperative time. Long-term immunosuppression after kidney transplantation can lead to complications, such as adverse drug reactions, opportunistic infections and malignancies, all of which are key concerns for management.

3.2.1 Focus of early follow-up

Early follow-up is performed within 3 months after renal transplantation. The patients are followed up 1-2 times a week within the first month post-transplantation and once every 1-2 weeks in the 2-3rd months post-transplantation.

3.2.1.1 What physicians concerned about

The assessment is based on the patient's condition and requires an assessment of immunosuppressant therapy, including the achievement of plasma concentration and determination of rejection reactions. Annual screening should include dermatological and cardiovascular examinations, and the recipients should also be subjected to routine examination programs, special types of examinations and tumor screening.

Routine tests include routine blood and urine test, blood biochemistry (liver function, kidney function, blood glucose, blood lipids), urine microalbumin, 24h Urine protein measurement, immunosuppressant plasm concentration and ultrasound of allograft kidneys. Special tests include lymphocyte subset tests, immunoglobulin series tests, virus tests (e.g., BK virus, cytomegalovirus, EB virus, JC virus, hepatitis B virus, hepatitis C virus), panel reactive antibody, donor-specific antibodies.

Tumor screening includes imaging tests such as chest X-ray film or lung CT, ultrasound of the abdomen, urinary system and thyroid. Female patients may undergo breast and gynecologic ultrasound and be examined for tumor markers.

3.2.1.2 What pharmacists concerned about

The medication history of the patients is collected for drug reorganization, and the indication of drug use, whether the drug administration plan is reasonable and the administration method is correct are reviewed; monitor blood concentration of drugs, evaluate the therapeutic effects and safety of drugs, and make recommendations for modification of dosing regimens when necessary; identify, resolve, and prevent drug-related problems; report and manage (suspected) adverse drug events; manage potential or actual drug-drug or drug-food interactions; compliance education.

3.2.1.3 Content of medication education for patients

Fully communicate with the recipients, repeatedly explain issues related to medication administration, self-monitoring, timely follow-up, and timely consultation,and explain the clinical effect of each drug. Recipients should take anti-rejection drugs and other adjuvant drugs on time and in the right dosage, and be familiar with the names, doses, purposes and adverse effects of the drugs, especially calcineurin inhibitors (e.g., CsA, Tac). The urine volume and the status of the allograft kidneys should be observed daily, and the body weight, body temperature, blood pressure and pulse should be monitored and recorded. Attention should be paid to a

reasonable diet and infection prevention after renal transplantation.

3.2.2 Focus of interim follow-up

Interim follow-up is performed once every 2-4 weeks in the 4-6th months post-transplantation.

3.2.2.1 What physicians concerned about

The focus of this phase of follow-up is the timely detection and management of acute rejection reactions and various infections (especially pulmonary infections). According to the patient's individual situation, follow-up examinations such as routine examinations, special types of examinations and tumor screening are selectively prescribed.

3.2.2.2 What pharmacists concerned about

It is necessary to strengthen the monitoring of the blood concentration of immunosuppressants, timely adjust the dosage of drugs, develop personalized drug regimens, and guard against rejection reactions and drug toxicity; at the same time, the monitoring of adverse reactions to immunosuppressants should be strengthened, focusing on events such as hypertension, hyperglycemia, hyperuricemia and dyslipidemia.

3.2.2.3 Content of medication education for patients

At this stage, the blood concentrations of immunosuppressants are still in the intensive adjustment period, the immune function of the body is still at a low level, and the risk of pulmonary infection is greater; therefore, the recipients should be informed to strengthen the prevention and self-monitoring of pulmonary infection.

3.2.3 Focus of long-term follow-up

Long-term follow-up refers to the follow-up after 6 months post-transplantation. The patients are followed up once a month in the 7-12th month post-transplantation; once a month or twice a quarter in the 13-24th month; every 1-2 months from 3rd to 5th year, and at least once every quarter after 5 years post-transplantation. For recipients with unstable graft function, follow-up frequency should be increased as appropriate.

3.2.3.1 What physicians concerned about

At this stage, the immunosuppressant dose is at the maintenance level, and the ability of the recipient to resist infection is gradually recovering, allowing him to resume normal life and work. The key points of follow-up at this stage are as following: focusing on the monitoring and prevention of cardiovascular diseases, infections, and malignant tumors, actively dealing with abnormalities of hypertension and metabolic indicators, and selectively prescribing follow-up examinations such as routine examinations, special types of examinations and tumor screening examinations according to the individual conditions of patients.

3.2.3.2 What pharmacists concerned about

One third of patients with late graft loss can be attributed to noncompliance with medication, which is an important factor leading to chronic rejection. Pharmacists should carry out patient education to eliminate the complacency that is common in transplant recipients at this stage, and should require recipients to come to the clinic for regular follow-up visits, emphasize strict adherence to medication administration orders and strictly prohibit self-reduction or withdrawal of drugs. Pharmacists should report and manage (suspected)

adverse drug events; manage potential or actual drug-drug or drug-food interactions; inform recipients that smoking can lead to cardiovascular disease and increase the risk of tumors after kidney transplantation, and advise smokers to quit. Attention should also be paid to the various complications of chronic kidney disease, such as anemia, acidosis, and bone disease[92].

3.2.3.3 Content of medication education for patients

Non-adherence to immunosuppressants therapy may lead to graft rejection and it is a major disadvantage in the treatment process after transplantation. High cost of drug therapy, large number of drugs, complexity of therapy regimens, patients' incomprehension and fear of drug therapy regimen and adverse drug reactions are the main reasons for patients' non-adherence to drug therapy. Care should be taken to educate patients to be aware of this. It is particularly important for post-transplant patient care that pharmacists explain the nature and effects of the immunosuppressants to patients to enhance their awareness of potential drug side effects and to ensure patient compliance with their drug regimen.

3.3 Patient medication guidance and management of adverse reactions

3.3.1 Immunosuppressant medication guidance

3.3.1.1 Immunosuppressants must be taken at a fixed time point.

The time of administration should not vary by more than 20 min, and should be taken on an empty stomach (1 h before meals). Patients should report in time in case of missed dose, vomiting or diarrhea, so that the medications can be adjusted and replenished appropriately.

3.3.1.2 Treatment to manage missed immunosuppressants after transplantation

If the time between the missed dose and the next dose is less than 4 h, the full dose should be taken immediately and the next dose should be postponed by 2 h. If the time between the missed dose and the next dose is 4-6 h, the full dose should be taken as early as possible and the next dose should be reduced by half. If the time between the missed dose and the next dose is more than 6 h, the half dose should be taken as early as possible and the next dose should be postponed appropriately. The interval between two doses should not be less than 8 h.

3.3.1.3 Treatment of vomiting after taking immunosuppressants post-transplantation

If vomiting occurs within 10 min after immunosuppressant treatment, a full dose should be added; if vomiting occurs within 10-30 min, 1/2 dose should be added; if vomiting occurs between 30-60 min, 1/4 dose should be added; if vomiting occurs more than 60 min, no additional dose is needed.

3.3.2 Pay attention to the combination of medications and interactions in patients

Transplantation recipients are often accompanied by bacterial and fungal infections, osteoporosis, hypertension, hyperglycemia, hyperuricemia and dyslipidemia, which often require the combination of multiple drugs, and there is a risk of interaction and multiple drug use. In addition, some health products, traditional Chinese medicine and food commonly taken by patients have interaction risks with immunosuppressants, which need to be paid attention to. If necessary, medication orders can be reformed or prescriptions can be simplified.

Recipients in the early post-transplant period should insist on taking compound sulfamethoxazole tablets as prescribed to prevent Yersinia pneumoniae infection (use with caution or as prescribed by the physician in patients with favism), paying attention to potential interactions; recipients who use Wuzhi preparations, such as Wuzhi tablets, Wuzhi capsules, Wuzhi softgels, and Wuzhi dropping pills, which can significantly affect the blood concentration of Tac and CsA, must ensure that they take these medications on time and in the right amount. Different Wuzhi products cannot be replaced at will, and if the drug is replaced, the drug concentration should be monitored. Patients should try to avoid foods that cause changes in Tac blood concentration such as grapefruit and avoid taking unused proprietary Chinese medicines or herbal medicines.

3.3.3 Management of adverse reactions in patients

Because the mechanisms of action of various immunosuppressants are different and the severities of adverse reactions are mostly related to the doses or blood concentrations, most of the adverse reactions can be relieved after stopping or reducing the dose. The monitoring of blood concentration should be strengthened during use, and the management of pharmacological monitoring should be strengthened for special patients, and the clinical manifestations, liver and kidney function and other indicators should be closely monitored. CNI dose reduction should be considered in transplant patients using CNI drugs if pathological puncture shows interstitial fibrosis and tubular atrophy in allograft kidneys, or if CNI toxicity is confirmed [92].

3.3.3.1 Common adverse reactions of drugs

(1) Glucocorticoids

Glucocorticoids can induce or aggravate infection; predispose patients to post-transplant diabetes and osteoporosis, metabolic bone disease; hinder tissue repair, delay granulation tissue formation, hinder healing of surgical wounds, trauma and other ulcers; long-term use may cause centripetal central obesity, full-moon face, buffalo back hump, hirsutism, acne, peptic ulcers, muscle atrophy and weakness, hypertension, hyperlipidemia, growth inhibition in children and hyperalgesia.

(2) CsA

Approximately 25%-38% of CsA recipients have developed dose-related nephrotoxicity, which include increased serum creatinine levels, decreased glomerular filtration rates. Chronic and progressive renal injury can occur at about one year after CsA treatment. 4% of renal transplantation recipients may develop hepatotoxicity manifested as elevated liver enzymes and bilirubin. The hepatotoxicity usually happens in the first month of administration with high-dose CsA and decreases after CsA dose reduction. The common adverse events include neurotoxicity which is manifested as impaired consciousness, convulsions, visual disturbances, loss of motor function, dyskinesia, and psychiatric disorders. Some patients receiving CsA have adverse events including hyperkalemia, gastrointestinal reactions (e.g., anorexia, nausea and vomiting), hirsutism, gingival hyperplasia with bleeding and pain. Allergic reactions, pancreatitis, leukopenia, Raynaud's syndrome, diabetes mellitus and hematuria are less common adverse reactions. Additionally, CsA is associated with an increased risk of lymphoma and other malignant tumors.

(3) Tac

The more frequent adverse events are opportunistic infections (e.g., polyomavirus infection and cytomegalovirus), neurological reactions (e.g., headache, insomnia, weakness, tremor, and abnormal

sensation), and gastrointestinal reactions (e.g., nausea, vomiting and diarrhea). Other common adverse events include hypertension and leukocytosis. The toxicities of kidney and liver, nephrotoxic reactions, hyperkalemia and hypomagnesemia may occur, and islet cytotoxicity of Tac can lead to secondary hyperglycemia. There is an increased risk of lymphoma and other malignancies in patients receiving Tac.

(4) MMF and mycophenolate sodium

Adverse events include opportunistic infections such as cytomegalovirus and herpes virus infections; the incidence of myelosuppression such as leukopenia in peripheral blood is around 2%, which should be closely monitored during the administration, especially at the beginning. Common gastrointestinal reactions (e.g., nausea, vomiting and diarrhea) are mostly dose-dependent. When combined with other immunosuppresants, MMF and mycophenolate sodium may increase the risk of lymphoma and other malignant tumors (especially skin cancer).

(5) Azathioprine

The common adverse events include myelosuppression (e.g., leukopenia, thrombocytopenia and anemia), cholestasis and hepatic impairment. Additionally, azathioprine may cause skin rash and occasional amyotrophy.

(6) Mizoribine

Hyperuricemia is a common adverse reaction. Compared to azathioprine or anti-proliferative MMF, myelosuppressive effects on mizoribine such as thrombocytopenia and erythrocytopenia are less severe. Loss of appetite, nausea, vomiting, abdominal pain, and diarrhea may occur occasionally.

(7) Leflunomide

The more common adverse events are diarrhea, pruritus, reversible elevations of alanine aminotransferase and aspartate aminotransferase, hair loss, skin rash, and decreased white blood cells.

(8) Sirolimus

The most frequent adverse reaction is hyperlipidemia, the mechanism of which is still unclear. The risk of angioedema is increased when sirolimus is combined with angiotensin converting enzyme inhibitors. Sirolimus is closely associated with the development of proteinuria, especially in recipients with diabetes mellitus after conversion. It is possible to induce sirolimus-related interstitial pneumonia. Moreover, sirolimus can lead to myelosuppression, poor incisional healing, peripheral edema, lymphedema, pleural effusion, and pericardial effusion. Sirolimus is shown to increase the incidence of infection and may possibly induce lymphoma and skin malignancies.

3.3.3.2 Management of postoperative complications

(1) Patients with diabetes mellitus

For patients who develop or are at high risk of post-transplant diabetes mellitus, an early glucocorticoid withdrawal strategy with close monitoring of Tac blood concentrations is recommended. After the first month post-transplantation, the withdrawal of corticosteroids may be considered for stable recipients without rejection, while Tac dosage is reduced and lower blood levels (4-7 μg/L) are maintained, to improve or reverse

glucose metabolism disorders. Patients should have regular testing of blood glucose and lipid levels as well as annual screening for diabetic complications such as microalbuminuria, diabetic nephropathy, and retinopathy [2, 93, 94].

(2) Patients with hyperlipidemia

CsA, sirolimus and corticosteroids can elevate blood lipid levels. Since Tac has a low effect on blood lipid, it is recommended for patients with hyperlipidemia to take a Tac-based immunosuppressive regimen, as well as consider to reduce or withdrawal corticosteroids. If the hyperlipidemia after transplantation is confirmed to be associated with the use of immunosuppresants and the transplanted kidneys are functionally stable, it can be considered to take a replacement of CsA with Tac or take a regimen of reduced dose of CNI combined with mycophenolic acid. Sirolimus should be administrated with caution in severe dyslipidemia. Dyslipidemia can occur as early as the first 3 months after transplantation, with the highest incidence of dyslipidemia occurring at the 6th to 9th months post-transplantation. Therefore, patients' blood lipid levels should begin to be monitored during the pre- and peri-operative period, and be reviewed monthly within 6 months after transplantation. According to lipid levels and treatment effect, blood lipid as well as urine protein, should be monitored every 1-3 months from 7th to 12th months post-transplantation, and should follow up at least once a year [2, 93, 95].

(3) Patients with hypertension

The use of immunosuppresants is strongly associated with post-transplant hypertension, especially CNI and corticosteroids. Corticosteroids are an important factor of affecting post-transplant hypertension, but the effect tends to decrease with the application of a new immunosuppressive regimen. Tac has a less impact on post-transplant hypertension than CsA, therefore, the conversion to a Tac-based immunosuppressive regimen may be considered if hypertension is determined to be associated with CsA use. Sirolimus has a lesser effect on hypertension. Common immunosuppression modification regimens include: early post-transplant lower-dose CNI, CNI replacement and reduction or withdraw of corticosteroids. Patients should have regular physical and laboratory examinations [2, 93, 96].

(4) Patients with tuberculosis (TB)

Since rifamycin, a kind of antituberculosis drugs, has multiple drug interactions with immunosuppresants, it is suggested to treat active TB preferably before transplantation. For patients with non-severe TB, an anti-TB regimen without the combination of rifamycin may be considered as well as the use of rifapentine instead of rifampicin to reduce interactions with CNI and sirolimus [97,98]. Blood levels of CNI and sirolimus should be monitored during treatment. In kidney transplant patients who require concomitant rifampicin antituberculosis therapy, acute rejection can be induced by a sudden drop in Tac concentrations due to rifampicin. Additionally, for some patients, it is specially difficulty to achieve the desired Tac concentration even after increasing dose. Thus, the drug interaction between rifampicin and Tac has become an important cause of transplant kidney failure in TB patients. The additional administration of Wuzhi tablets can both increase the Tac blood concentration up to the therapeutic window to reduce the risk of acute rejection, and keep the anti-tuberculosis treatment with rifampicin [99]. Post-transplant TB reminds lower immune function of patients. Under the premise of stable transplanted kidney without adverse reactions to anti-tuberculosis drugs, effective anti-tuberculosis therapy should be administered with sufficient quantity and duration as much as possible. Further, it is not advised to reduce dose of anti-tuberculosis drugs only due to drug

interactions or deliberately increase the concentration of CNIs. The function of the transplanted kidney, T-lymphocyte subpopulation and urinary routine can be monitored dynamically to promptly adjust treatment regimens when changes are detected [97, 98].

3.4 Medication instructions for pregnant and lactating patients

If female or male patients receiving transplant immunosuppressive therapy have fertility needs, they should receive preconception counseling, carry out pregnancy and delivery under the guidance of physicians or pharmacists. It needs to pay an attention to drugs' impact on fetal malformations and choose the lowest effective dose as far as possible. Meanwhile, pharmacokinetic factors (e.g., volume of distribution, metabolism) are altered in patients during pregnancy, thus requiring more frequent monitoring and adjustment of drug concentrations.

3.4.1 Relatively safe drugs with low risk of fetal malformation

(1) Recommendations for hormone use: Prednisone and methylprednisone are relatively safe to use in all periods of pregnancy. Methylprednisone has a similar placental transfer rate to that of prednisolone, but doses less than 15 mg/d (prednisone or its equivalent) are preferred. The use of glucocorticoids containing fluoride in their structures should be avoided in early pregnancy, such as dexamethasone and betamethasone. Both prednisone and methylprednisone can be used during breastfeeding. However, breastfeeding should be avoided within 4 h of prednisone administration if the dose is more than 20 mg/d [100-103].

(2) Recommendations for CsA use: CsA and Tac can increase the risk of neonatal complications such as low body mass infants and intrauterine growth retardation, but there is no increased risk of the incidence of congenital malformations in the fetus. It is relatively safe to use the lowest effective dose of CsA throughout pregnancy. Mothers taking CsA should not be prevented from breastfeeding, which can be allowed when the benefits outweigh harms to the infant [100-102].

(3) Recommendations for Tac use: It is relatively safe to use the lowest effective dose of Tac throughout pregnancy. Tac is excreted in breast milk, but the amount in breast milk is only 1% of the maternal dose, and the proportion reaching the newborn is even lower. Mothers taking Tac should not be prevented from breastfeeding, which can be allowed when the benefits outweigh harms to the infant [100-102].

(4) Recommendations for azathioprine use: It is relatively safe to use azathioprine at doses less than 2 mg/kg during pregnancy [100, 103-105]. Although azathioprine may not increase the risk of teratogenicity, there is an increased incidence of other pregnancy complications (e.g., low birth mass, preterm delivery and jaundice [104]). The excretion of azathioprine in breast milk is very low, so lactating women may appropriately continue azathioprine for medical necessity and breastfeeding after 4 h of use [100, 103, 106, 107].

3.4.2 Drugs with a high risk of fetal malformation, needed to be avoided or used with caution

(1) MMF and mycophenolate sodium: MMF and mycophenolate sodium increase the risk of early miscarriage and congenital malformations during pregnancy. Abnormal limb and face are the most common congenital malformations. Both medicines are contraindicated during pregnancy. They should be discontinued at least 3 to 6 months prior to planned pregnancy or egg retrieval, which may be replaced with azathioprine at doses not exceeding 2 mg/kg [100, 103-105]. There are no available data on the excretion of MMF and mycophenolate sodium in breast milk, therefore, it is not recommended to use these drugs during

breastfeeding [100-102].

(2) Leflunomide: Leflunomide contraindicated during pregnancy, should be discontinued to use more than 2 years prior to conception or combine with chelating agents to reduce blood concentration to <0.02 mg/L before pregnancy. In addition, it is not recommended for use during breastfeeding [100-102].

(3) Sirolimus: Sirolimus is a drug that does not exclude risk in humans. According to animal studies, it has been associated with increased mortality, weight loss, and delayed ossification. Although no teratogenic effect has been found, sirolimus remains contraindicated during pregnancy., It has insufficiently available evidence that breastfeeding for women taking sirolimus is safe, thus, breastfeeding should be avoided [100-102].

4 Patients' health management

In addition to regular follow-up management, it is crucial for kidney transplant recipients to receive instructions on healthy living and assessment of psychological and behavioral changes.

4.1 Lifestyle guidance

The guidance for transplant recipients on diet, exercise, work and rest should be strengthened. It is suggested to quit smoking as well as alcohol, inform patients of the herbal medicines they should not take and be cautious with herbal formulas or supplements (ginseng and ganoderma lucidum) and fruits such as grapefruit and star fruit (which increases nephrotoxicity). Excessive oil or cold foods that cause diarrhea should be avoided. It is recommended that patients adhere to a low-sugar, low-fat, high-fiber and high-quality protein diet, including eggs, fish, poultry, pork and beef; as well as consume more fresh vegetables and fruits, no or less fried or deep-fried food, hot pot, barbecue, pickled food and animal offal.

4.2 Prevention of infection

In the early postoperative period and during the influenza season, patients should minimize visits to places where people are concentrated and with poor ventilation facilities (such as supermarkets and vegetable markets); pay attention to keeping warm in cold weather and avoid contacting with flu patients ; keep living room clean and well ventilated, change clothes regularly, do not go to damp and cold environments, do not read old newspapers and books, do not unpack and wash old quilts, etc.; get vaccinated against influenza, novel coronavirus and herpes virus if necessary.

4.3 Psychological guidance

Most of the transplant recipients' life qualities have significantly improved compared to the preoperative period and are basically the same as normal people. A series of psychological changes in a small number of patients such as anxiety, depression, and autism, should be emphasized, which are caused by unemployment, economic problems, singleness, and postoperative complications. These psychological changes may affect medication adherence and health recovery. Attention should be paid to the assessment of the patients ' behavior and their reflected psychological problems, and guidance should be provided timely. Psychological experts can be invited for psychological counseling if necessary.

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