Tacrolimus in preventing transplant rejection in Chinese patients – optimizing use

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Abstract: Tacrolimus is a product of fermentation of Streptomyces, and belongs to the family of calcineurin inhibitors. It is a widely used immunosuppressive drug for preventing solid-organ transplant rejection. Compared to cyclosporine, tacrolimus has greater immunosuppressive potency and a lower incidence of side effects. It has been accepted as first-line treatment after liver and kidney transplantation. Tacrolimus has specific features in Chinese transplant patients; its in vivo pharmacokinetics, treatment regimen, dose and administration, and adverse-effect profile are influenced by multiple factors, such as genetics and the spectrum of primary diseases in the Chinese population. We reviewed the clinical experience of tacrolimus use in Chinese liver- and kidney-transplant patients, including the pharmacology of tacrolimus, the immunosuppressive effects of tacrolimus versus cyclosporine, effects of different factors on tacrolimus metabolism on Chinese patients, personalized medicine, clinical safety profile, and patient satisfaction and adherence. This article provides guidance for the rational and efficient use of tacrolimus in Chinese organ-transplant patients.

Keywords: tacrolimus, liver transplantation, kidney transplant, Chinese, personalized medicine

Introduction

Organ transplantation is the treatment of choice for patients with end-stage organ failure. Kidney and liver transplantation accounts for greater than 90% of all large-organ transplants in the People’s Republic of China (PRC). According to data published by the Chinese Scientific Registry of Kidney Transplantation, 6,471 kidney transplants were performed in the PRC in 2013. The China Liver Transplant Registry gathered data on 20,818 patients who underwent liver transplantation between February 2005 and December 2011. Although the PRC is the second-largest country after the United States (US) with regard to the annual number of organ transplants, only 10,000 transplants are actually performed per year in the PRC. However, approximately 300,000 patients require organ transplantation annually; many die due to shortage of donor organs. Increasing the success and long-term survival of grafts is an efficient way to offset donor organ shortage. Graft rejection is the primary cause of chronic loss of graft function in the PRC.1,2 The key to controlling graft rejection is appropriate immunosuppression. Immune-induction therapy, either intravenous antilymphocyte globulin or anti-IL-2 receptor monoclonal antibody and methylprednisolone pulse therapy, is frequently used in the perioperative period. Maintenance therapy includes dual-, triple-, or quadruple-therapy regimens, including cyclosporine A (CsA) or tacrolimus (FK506) as the main components (CsA or tacrolimus plus mycophenolate mofetil [MMF] plus prednisone) to prevent acute rejection.3 Tacrolimus was first used in organ transplantation in the PRC in the late 1990s.4 With greater immunosuppression and a...
more favorable safety profile over CsA, tacrolimus gradually became the preferred immunosuppressant after liver and kidney transplantation, in place of CsA. This article reviews the clinical utility of tacrolimus in the PRC.

**Pharmacology, mode of action, and pharmacokinetics of tacrolimus**

In 1984, tacrolimus, a macrolide lactone antibiotic, was isolated from the fermentation broth of *Streptomyces tsukubaensis* and was considered a novel immunosuppressant.\(^5\) In vitro animal experiments subsequently revealed that tacrolimus had a strong immunosuppressive effect.\(^6\,^7\) In 1989, the use of tacrolimus for the prevention of rejection in liver transplantation was published.\(^8\) In 1994, the US Food and Drug Administration approved the use of tacrolimus in liver transplantation.\(^9\,^10\) Its use has since expanded to other organ types, and today it is the most widely used posttransplant immunosuppressant medication.

There are two main patterns of graft rejection following organ transplantation: acute and chronic rejection. During the process of graft rejection, T cells, B cells, and cytokines play important roles. T cells recognize the antigens of donors and are activated to proliferate, differentiate, and secrete cytokines. These cytokines stimulate B cells to produce antigrant antibodies. These cytokines also help cytotoxic T cells to develop cytotoxicity against the graft. The antigens of the graft are recognized by T-cell receptors; this stimulation induces generation of the second messengers of T cells. The activation of second messengers results in a sustained high level of intracellular calcium. Calcium activates calcineurin phosphatase, which changes the cytoplasmic component of nuclear factor and transports it into the nucleus. Then, transcription factor is formed, which can activate IL-2 gene transcription. IL-2 can induce T-cell proliferation and activation. Activated T cells secrete different types of cytokines. IL-2 also increases cytotoxic T-cell activity.\(^11\) Tacrolimus can form a complex with immunophilin FK-binding protein 12. This complex strongly inhibits calcineurin phosphatase activity and inhibits IL-2 expression. Subsequently, T-cell activation and cytokine secretion are inhibited. This is the mechanism by which tacrolimus prevents allograft rejection (Figure 1).

Tacrolimus is absorbed in the gastrointestinal tract, reaching peak blood concentrations in 1–3 hours, with a mean bioavailability of approximately 20%–25%.\(^12\) Tacrolimus mainly binds to erythrocytes. In the plasma, 99% of tacrolimus is bound to α1-acid glycoprotein. The blood/plasma tacrolimus-distribution ratio is about 20:1. Tacrolimus is the substrate of cytochrome P450 (CYP)-3A isoenzymes and P-glycoprotein. Tacrolimus is metabolized mainly by CYP3A4 and CYP3A5 in the liver and intestinal epithelium.\(^13\) P-glycoprotein, also known as multidrug-resistance protein (MDR)-1 or adenosine triphosphate-binding cassette subfamily B member 1, is an adenosine triphosphate-dependent efflux pump. It is expressed in intestinal epithelium cells, limiting the absorption of tacrolimus, and in the bile canalicular membrane of hepatocytes, mediating the biliary elimination of tacrolimus.\(^14\)

Tacrolimus has wide interindividual variability in its pharmacokinetics. The maximum area under the curve (AUC) of tacrolimus was almost four times higher than the minimum AUC after the first oral dose in combination with MMF and prednisone among Chinese renal transplant recipients.\(^15\) In addition, it is characterized by a narrow therapeutic index. Underdosage of tacrolimus may result in graft rejection, while overdosage may result in toxicity.\(^16\,^17\) In order to avoid adverse effects, therapeutic drug monitoring (TDM) of tacrolimus whole-blood trough concentrations is necessary. In Europe and the United States, AUC-based tacrolimus TDM has been widely used. AUC, the best marker of exposure to tacrolimus, is calculated based on a limited sampling strategy using Bayesian estimation. The dose of tacrolimus is adjusted to reach the AUC target.\(^18\) In the PRC, most hospitals have been using trough blood concentrations for routine dose adjustment of tacrolimus. The proposed initial dose of tacrolimus is approximately 0.10–0.20 mg/kg per day in adult liver-transplant recipients, and 0.15–0.30 mg/kg per day in adult kidney-transplant recipients, and is taken orally twice daily, 1 hour before meals or 2 hours after meals.\(^19\)

The recommended target trough blood concentration for Chinese renal transplant recipients is 12–15 ng/mL for the first month after transplantation, 8–12 ng/mL for the second month, 6–10 ng/mL for the third month, and 5–10 ng/mL for the fourth month after transplantation. The sustained concentration after 1 year.

The recommended starting dose for tacrolimus in Chinese pediatric renal allograft recipients is 4.7–5.6 mg/m\(^2\) per day, with a maintenance dose of 0.93–1.56 mg/m\(^2\) per day.\(^22\) Owing to interindividual variability, it can take several weeks for the dosage to achieve therapeutic efficacy; transplant recipients have a significant risk of side effects during this period. Therefore, it is paramount to achieve a stable maintenance dose as soon as possible after transplantation.\(^23\)
Several factors can affect tacrolimus pharmacokinetics. In a study of 142 Chinese renal transplant recipients, tacrolimus maintenance dose negatively correlated with hematocrit, hemoglobin, total bilirubin, and indirect bilirubin, and positively correlated with body weight. In another study of 262 Chinese adult liver-transplant recipients, clearance of tacrolimus significantly correlated with hematocrit and total plasma protein. In addition, it has been reported that grapefruit juice can increase tacrolimus concentration in Chinese liver-transplant patients.

Furthermore, drug–drug interactions can also affect tacrolimus pharmacokinetics.

In addition to these factors, genetic factors play an important role in the variability of tacrolimus pharmacokinetics. A series of studies revealed that CYP3A5 6986A>G (CYP3A5*3) had a significant impact on tacrolimus pharmacokinetics in Chinese renal transplant recipients. Patients with CYP3A5*3/*3 had higher C₀/D (dose-corrected tacrolimus trough concentrations) compared with patients with CYP3A5*1/*3 or CYP3A5*1/*1. Two studies found that
CYP3A4*1G was significantly associated with tacrolimus pharmacokinetics in Chinese renal transplant recipients. Patients with CYP3A4*1*/1 had higher C\textsubscript{0}/D and lower tacrolimus clearance compared with patients with CYP3A4*1*/1G or CYP3A4*1*/1G. Li et al\textsuperscript{13} found that CYP3A4*18B may be partly responsible for the large interindividual variability of tacrolimus blood levels in Chinese renal transplant patients during the first month after transplantation. However, in a study of 227 Chinese renal transplant patients, Zhu et al\textsuperscript{19} found no significant association between the C\textsubscript{0}/D of tacrolimus and CYP3A4*18B genotypes when they were classified by the different CYP3A4 genotypes.

Regarding the relationship between MDR1 polymorphisms and tacrolimus pharmacokinetics, there were inconsistent results in Chinese renal transplant recipients. Several studies revealed that the MDR1 3435C>T had a significant effect on the C\textsubscript{0}/D of tacrolimus (P<0.05). MDR1 3435CC patients displayed a lower tacrolimus level per dose than MDR1 3435CC/TT patients.\textsuperscript{34–36} Nevertheless, other studies failed to find a significant association between the MDR1 3435T>C polymorphism and tacrolimus pharmacokinetics. An outline of the genetic polymorphisms affecting tacrolimus pharmacokinetics in Chinese renal transplant patients is presented in Table 1.

The liver is the organ in which tacrolimus is metabolized. Therefore, donor genetics may also affect tacrolimus pharmacokinetics in Chinese liver-transplant patients. Several studies revealed significantly higher tacrolimus C\textsubscript{0}/D in donors with CYP3A5*3/*3 compared with CYP3A5*1/*3 or CYP3A5*1/*1 (P<0.05), and no significant difference of tacrolimus C\textsubscript{0}/D was observed in recipients with different CYP3A5 genotypes.\textsuperscript{39–41} However, other studies reported that recipient CYP3A5*3 was also significantly associated with tacrolimus C\textsubscript{0}/D.\textsuperscript{42–44} A series of studies reported that recipient MDR1 3435T>C significantly affected tacrolimus pharmacokinetics in Chinese liver-transplant patients. A lower daily tacrolimus dose or higher C\textsubscript{0}/D was observed in recipients carrying the MDR1 3435T allele, compared with 3435CC recipients at different times after transplantation.\textsuperscript{40,45–47} Correspondingly, two other studies found that recipient MDR1 3435T>C was not associated with tacrolimus C\textsubscript{0}/D in Chinese liver-transplant patients.\textsuperscript{41,43} Moreover, no correlation has been observed between tacrolimus daily dose or C\textsubscript{0}/D and donor MDR1 3435T>C in any of the published studies until now.\textsuperscript{40,41,45,46} Li et al\textsuperscript{13} reported that the IL-10 1082G>A of recipients can affect tacrolimus pharmacokinetics. Recipients with the homozygous variant IL-10 -1082AA genotype had higher tacrolimus C\textsubscript{0}/D compared with the IL-10 -1082GG and GA genotype, and the IL-10 1082G>A of the donors had no significant association with tacrolimus C\textsubscript{0}/D. Nevertheless, another study found that the IL-10 1082G>A of donors can affect tacrolimus C\textsubscript{0}/D, and the same variant of recipients did not significantly influence tacrolimus C\textsubscript{0}/D.\textsuperscript{48} In addition to these genetic variants, it has been reported that donor TLR4 rs1927907G>A and IL6 rs1800796 G>C were also closely associated with tacrolimus elimination in Chinese liver-transplant patients.\textsuperscript{42–44} An outline of the genetic polymorphisms affecting tacrolimus pharmacokinetics in Chinese liver-transplant patients is presented in Table 2.

Currently, two studies have individualized the first oral dose of tacrolimus on the basis of the CYP3A5 genotype in Chinese renal transplant patients. Zhang et al\textsuperscript{49} conducted a study of 76 Chinese renal transplant recipients within two successive periods. In the first period, 0.1 mg/kg/day of tacrolimus was the initial dose prescribed for 28 recipients, regardless of their CYP3A5 genotype. In the second period, another 48 recipients were prescribed the following doses according to their genotypes: 0.08 mg/kg/day for CYP3A5*3/*3 (CYP3A5 non-expresser) and 0.15 mg/kg/day for CYP3A5*1/*3 (CYP3A5 expresser). Adjustment of the initial dosage of tacrolimus was documented to improve the proportion of patients achieving target drug blood levels in the early postoperative stage: from 46.7% to 81.8% of the *1/*3 group, and from 46.2% to 73.1% of the *3/*3 group on the third day. Another prospective study, by Chen et al\textsuperscript{10} also confirmed the efficiency of CYP3A5 genotype-guided use of tacrolimus in Chinese renal transplant recipients. The study consisted of two parts. In the first part, 120 patients received routine initial doses of tacrolimus (0.06 mg/kg every 12 hours). Pharmacokinetic data from these patients were used to fit a regression equation that predicted tacrolimus initial dose on the basis of the CYP3A5 genotypes. In the second part, patients received initial doses of tacrolimus according to the equation derived from the first part. The results demonstrated that genotype-guided dosing could significantly decrease the incidence of out-of-range tacrolimus levels. Therefore, initial tacrolimus-dosage selection based on CYP3A5 genotype can improve the proportion of patients achieving target trough blood concentrations in Chinese renal transplant recipients.

However, besides genetic factors, other factors can also affect tacrolimus pharmacokinetics. Li et al\textsuperscript{19} developed a tacrolimus-dosing model to predict the initial dosage for Chinese renal transplant patients based on both genetic and clinical factors. However, this model has not been evaluated in clinical practice. Determining additional genetic factors of variability among Chinese individuals in response to tacrolimus and developing the tacrolimus-dosing model are very important to improve therapeutic and clinical efficacy in Chinese transplant patients.
Table 1 Effect of different gene polymorphisms on tacrolimus pharmacokinetics in Chinese renal transplant patients

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<tr>
<td>Zhao et al28</td>
<td>Kidney recipients</td>
<td>CYP3A5*3 and *6</td>
<td>Patients with the CYP3A5*3/<em>3 polymorphisms required less tacrolimus to reach target concentrations compared to those with the CYP3A5</em>1 allele.</td>
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<td>Chen et al25</td>
<td>Kidney recipients</td>
<td>CYP3A5*3</td>
<td>CYP3A5<em>3 influenced the blood concentrations of tacrolimus. This study suggested that the initial dosage be chosen according to the CYP3A5</em>3 genotype.</td>
</tr>
<tr>
<td>Zhang et al26</td>
<td>Kidney recipients</td>
<td>CYP3A5*3</td>
<td>CYP3A5<em>3 played an important role in influencing tacrolimus blood levels. Initial tacrolimus dosage selection based on CYP3A5</em>3 genotype could improve drug blood levels in the early stage following renal transplantation.</td>
</tr>
<tr>
<td>Chen et al27</td>
<td>Kidney recipients</td>
<td>CYP3A5*3</td>
<td>CYP3A5 expressers (CYP3A5*1/<em>1 and CYP3A5</em>1/*3) needed more tacrolimus to reach therapeutic concentration window.</td>
</tr>
<tr>
<td>Zhu et al30</td>
<td>Kidney recipients</td>
<td>CYP3A4*1G</td>
<td>Patients with CYP3A5*1/*1 and *1/<em>3 genotypes were significantly lower than those with CYP3A5</em>3/<em>3 genotypes. No significant association was found between the C/C of tacrolimus and CYP3A4</em>1G genotypes when they were classified by two CYP3A5 genotypes.</td>
</tr>
<tr>
<td>Zuo et al31</td>
<td>Kidney recipients</td>
<td>CYP3A4*1G</td>
<td>CYP3A5<em>3, CYP3A4</em>1G, and hematocrit were determining factors in the apparent clearance of tacrolimus.</td>
</tr>
<tr>
<td>Li et al32</td>
<td>Kidney recipients</td>
<td>CYP3A4*1G</td>
<td>CYP3A5<em>3 and CYP3A4</em>1B may be partly responsible in large interindividual variability of tacrolimus blood levels in Chinese renal transplant patients during the first month after transplantation.</td>
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<tr>
<td>Rong et al37</td>
<td>Kidney recipients</td>
<td>CYP3A5*3 and MDR1 3435C&gt;T</td>
<td>Renal transplant recipients who were CYP3A5<em>1 carriers required a higher dose of tacrolimus than CYP3A5</em>3/*3, indicating a significantly lower dose-adjusted AUC0-24 of tacrolimus. In contrast, MDR1 3435C&gt;T polymorphism was not an important factor in tacrolimus pharmacokinetics.</td>
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<tr>
<td>Zhang et al38</td>
<td>Kidney recipients</td>
<td>CYP3A5*3 and MDR1 3435C&gt;T</td>
<td>CYP3A5*3 polymorphisms were associated with tacrolimus pharmacokinetics and dose requirements in renal transplant recipients.</td>
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<tr>
<td>Li et al39</td>
<td>Kidney recipients</td>
<td>CYP3A5*3, MDR1 -129T&gt;C, 1236C&gt;T, 2677G&gt;T/A, 3435C&gt;T, and NR1I2 -25385C&gt;T</td>
<td>CYP3A5*3, body weight, hematocrit, hemoglobin, and total bilirubin significantly influenced the maintenance tacrolimus dose. MDR1 and NR1I2 gene polymorphisms were not significantly associated with maintenance tacrolimus dose.</td>
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<tr>
<td>Wu et al34</td>
<td>Kidney recipients</td>
<td>CYP3A5*3, CYP3AP1 -44G&gt;A, MDR1 1236C&gt;T, 2677G&gt;T/A, and 3435C&gt;T</td>
<td>Tacrolimus C/C was larger in CYP3A5*3 and CYP3AP1 nonexpressers than in expressers. Wild-type homozygotes for MDR1 C3435T had a slightly lower dose-adjusted C/D compared with heterozygotes. No significant association was found between MDR1 1236C&gt;T, 2677G&gt;T, or haplotypes and tacrolimus pharmacokinetics.</td>
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<tr>
<td>Li et al40</td>
<td>Kidney recipients</td>
<td>Seventeen polymorphisms of CYP3A5, CYP3A4, COMT, IL-10, and POR</td>
<td>CYP3A5<em>3, CYP3A4</em>1G, CYP3A4 rs4646437 T&gt;C, and IL-10 rs1800871C&gt;T might be potential polymorphisms affecting the interindividual variability in tacrolimus metabolism among Chinese renal transplant recipients.</td>
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<tr>
<td>Wang et al41</td>
<td>Kidney recipients</td>
<td>MDR1 2677G&gt;T/A and 3435C&gt;T</td>
<td>MDR1 2677G&gt;T/A and 3435C&gt;T were correlated with the whole blood concentration of tacrolimus.</td>
</tr>
<tr>
<td>Li et al42</td>
<td>Kidney recipients</td>
<td>MDR1 3435C&gt;T</td>
<td>MDR1 3435C&gt;T was associated with the tacrolimus concentration/dose ratio.</td>
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Abbreviations: AUC, area under the concentration–time curve; C/D, dose-corrected tacrolimus trough concentrations.
Table 2 Effect of different gene polymorphisms on tacrolimus pharmacokinetics in Chinese liver transplant patients

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<td>Yu et al 49</td>
<td>Liver recipients and donors (n=53)</td>
<td>CYP3A5*3</td>
<td>The tacrolimus C/D in patients with *1/*1 (*1/*3) genotype donors was significantly lower than in patients with *3/*3 genotype donors at 2 weeks (P&lt;0.036) and 1 month (P&lt;0.021).</td>
</tr>
<tr>
<td>Wei-lin et al 50</td>
<td>Liver recipients and donors (n=50)</td>
<td>CYP3A5*3 and MDR1 3435C&gt;T</td>
<td>The tacrolimus C/D were obviously lower in recipients carrying MDR1 3435C genotype. For CYP3A5 genotype, recipients who received organs from CYP3A5*3/*3 donors had higher C/D, but the donors' ABCB1 and recipients' CYP3A5 genotypes did not affect the recipients' pharmacokinetics.</td>
</tr>
<tr>
<td>Li et al 51</td>
<td>Liver recipients and donors (n=70)</td>
<td>TNF-α -308G&gt;A, IL-10 -1082G&gt;A, CYP3A5*3, MDR1 2677G&gt;T/IlA, and 3435C&gt;T</td>
<td>A significantly higher tacrolimus C/D was observed in recipients with the homozygous variant IL-10 -1082AA genotype, compared with the homozygous wild type IL-10 -1082GG genotype. The CYP3A5*3 variant in donors significantly influenced tacrolimus C/D during the first 3 weeks posttransplantation.</td>
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<tr>
<td>Shi et al 53</td>
<td>Liver recipients (n=216)</td>
<td>CYP3A5<em>3, CYP3A4</em>22, MDR1 3435C&gt;T, and 1236C&gt;T</td>
<td>Recipients CYP3A5*3 affected daily dose requirements, concentration, and nephrotoxicity of tacrolimus.</td>
</tr>
<tr>
<td>Wang et al 52</td>
<td>Liver recipients and donors (n=96)</td>
<td>CYP3A5*3 and TLR4 rs1927907G&gt;A</td>
<td>Both donor and recipient CYP3A5*3 allele A and donor TLR4 rs1927907 allele A were associated with a lower C/D during the early stage after transplantation.</td>
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<tr>
<td>Chen et al 54</td>
<td>Liver recipients and donors (n=96)</td>
<td>CYP3A5*3 and IL-6 rs1800796C&gt;C</td>
<td>Both donor and recipient CYP3A5<em>3 allele A showed association with lower C/D ratios, while donor IL-6 rs1800796 allele G showed an association with higher C/D ratios. Donor CYP3A5</em>3 allele A, IL-6 rs1800796 allele C, and recipient CYP3A5*3 allele A were associated with fast tacrolimus metabolism.</td>
</tr>
<tr>
<td>Jin et al 55</td>
<td>Liver recipients and donors (n=50)</td>
<td>MDR1 3435C&gt;T</td>
<td>Tacrolimus dose requirement and dose-adjusted trough levels were correlated with recipient's MDR1 3435C&gt;T polymorphism. No significant differences were found in tacrolimus doses or dose-adjusted trough levels according to the donor's MDR1 genotype.</td>
</tr>
<tr>
<td>Zhang et al 56</td>
<td>Liver recipients and donors (n=53)</td>
<td>IL-10 -1082G&gt;A, -819C&gt;T, -592C&gt;A, CYP3A5*3, MDR1 1236C&gt;T, 2677G&gt;T/IlA, and 3435C&gt;T</td>
<td>Donor CYP3A5*3/*3 was associated with higher tacrolimus C/D. In the first 2 weeks, the tacrolimus C/D ratios of the recipients with donors who were CYP3A5 nonexpressers and had a low IL-10 production genotype (-819TT, -592AA) were higher than those with donors who were CYP3A5 nonexpressers and had a high IL-10 production genotype (-819CC or CT, -592CC or AC),</td>
</tr>
<tr>
<td>Yu et al 57</td>
<td>Liver recipients (n=62)</td>
<td>MDR1 1236C&gt;T, 2677G&gt;T/IlA, and 3435C&gt;T</td>
<td>Recipients with C/T genotype at 3435C&gt;T had a little lower tacrolimus C/D compared to those with C/T and T/T genotypes (P=0.024).</td>
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</table>

Abbreviation: C/D, dose-corrected tacrolimus trough concentrations.

Efficacy studies

With the improvement in technology and accumulation of clinical experience, kidney and liver transplantation has progressed, with increased survival rates of grafts and Chinese transplant recipients. Chen et al. 43 analyzed the data of 1,806 Chinese renal transplant recipients between February 1984 and December 2003. The overall 1-, 5-, 10-, 15-, and 20-year patient-survival rates were 92.28%, 87.20%, 78.60%, 63.45%, and 47.59%, respectively. The 1-, 5-, 10-, 15-, and 20-year graft survival rates were 84.61%, 73.64%, 57.31%, 46.77%, and 31.18%, respectively. The overall half-life of transplanted kidneys was 11.94±0.84 years. In addition, some researchers compared the clinical efficacy of kidney transplant during the different periods. From 1983 to 1989, the 1-, 5-, and 10-year patient-survival rates were 87.8%, 68.3%, and 53.4%, respectively. From 1990 to 1998, the corresponding patient-survival rates were 90.6%, 84.9%, and 79.1%, respectively. The corresponding patient-survival rates were 98.9%, 94.0%, and 89.6% between 1999 and 2012. 31 Patient-survival rates increased with time. Hu et al. 42 analyzed
502 Chinese patients who underwent liver transplantation from 2000 to 2007, of whom 60.1% had malignant liver tumors. The overall 3-year survival rate in this group was 68.7%. Wang et al\textsuperscript{31} performed a retrospective study in a single medical center of 255 liver-transplant patients whose primary disease was hepatocellular carcinoma (HCC). The 1-, 2-, and 3-year patient-survival rates were 84.6%, 66.2%, and 52.6%, respectively; the 1-, 2-, and 3-year recurrence-free survival rates were 67.4%, 53.8%, and 47.3%, respectively. Recurrence of HCC is an important factor that influences long-term survival of Chinese liver-transplant patients.

Advancements in organ transplantation not only result from improvements in surgical technique but also benefit from the utility of immunosuppressive agents. It is particularly important for improving long-term survival of graft organs to choose a rational initial and maintenance immunosuppressive therapy regimen. So far, calcineurin inhibitors, including CsA and tacrolimus, are still the basic components of immunosuppressive regimens. There have been studies that suggested that tacrolimus is associated with a lower incidence of early stage rejection and fewer liver-toxicity events compared to CsA, therefore reducing the risk of chronic loss of graft function and cardiovascular disease while prolonging survival of patients and graft organs.\textsuperscript{33,54} The statistical data are shown in Table 3.

Yu et al\textsuperscript{39} performed a prospective study to investigate the efficacy of tacrolimus in Chinese kidney-transplant patients. Patients were randomly divided into tacrolimus (n=40) and CsA (n=50) groups. The incidence of rejection in the tacrolimus group decreased by 10% compared to the CsA group, and there were fewer toxicity events associated with tacrolimus. Acute and refractory rejection after transplant surgery is usually steroid-resistant. Favorable curative effects cannot be obtained by high-dose steroid pulse therapy in such patients. In this study, it was demonstrated that tacrolimus could reverse acute and refractory rejection in most cases. Another study also indicated the incidence of acute rejection within 1 year after renal transplantation in the tacrolimus group was 4.0%, while it was 15.6% in the CsA group (P<0.01).\textsuperscript{55}

Cheung et al\textsuperscript{46} performed a prospective randomized trial with paired kidney analysis to compare the efficacy of tacrolimus and CsA in reducing the incidence of 6-year postoperative long-term rejection of 76 Chinese kidney-transplant patients. The rates of acute rejection were significantly different between groups: 18.4% (7 of 38, tacrolimus group) versus 42.1% (16 of 38, CsA group) (P=0.03). Chronic allograft nephropathy (CAN) is the main reason for graft dysfunction. Ji et al\textsuperscript{47} conducted a 3-year follow-up study in 31 patients with pathologically diagnosed CAN. The authors suggested that conversion from a CsA-based regimen to a tacrolimus-based regimen could effectively improve renal function and delay the progression of CAN. This is comparable to another study including 73 patients with CAN conducted by Peng et al\textsuperscript{48} after 1 year of conversion, the level of serum creatinine in the CsA-tacrolimus group (n=43) was significantly lower than in the CsA group (n=30) (194.8±42.5 μmol/L versus 245.4±52.8 μmol/L, P<0.01). Meanwhile, the glomerular filtration rate in the CsA-tacrolimus group was significantly higher than in the CsA group. This indicated that tacrolimus improved renal function more effectively than CsA.

The population with hepatitis B virus (HBV) accounts for about 7% of the total Chinese population. The ratio of HBV-carrier kidney-transplant patients is even higher. Liu et al\textsuperscript{49} indicated that tacrolimus treatment caused less liver function impairment than CsA in HBV-carrier kidney-transplant recipients. In addition, another study suggested that a tacrolimus-based triple regimen in kidney-transplant patients with delayed graft function was associated with fewer adverse reactions and facilitated renal function recovery more effectively.\textsuperscript{60} Tacrolimus was also associated with a lower rejection rate in liver transplantation, and could reverse refractory transplant rejections, so tacrolimus should be the first choice for Chinese patients after liver transplantation.\textsuperscript{61} Ye et al\textsuperscript{62} investigated the relationship between serum tacrolimus concentration and clinical efficacy. They found that tacrolimus with 10–15 ng/mL whole blood concentrations not only effectively controlled rejection but also caused fewer adverse reactions.

In conclusion, tacrolimus is a highly effective immunosuppressive agent, and is suitable for Chinese liver- and kidney-transplant patients. Tacrolimus is superior to CsA in controlling rejection, reducing adverse reactions, and prolonging graft survival.

### Safety and tolerability

Tacrolimus has been used in Chinese organ-transplant practice for nearly 20 years, and has a good safety and tolerability profile. The short-term adverse effects of tacrolimus include posttransplantation diabetes mellitus, nephrotoxicity, neurotoxicity, and gastrointestinal effects. Symptoms include tremor, headache, diarrhea, and nausea; hyperglycemia and elevation of serum creatinine are additional effects. Xu et al\textsuperscript{43} analyzed data from 887 Chinese kidney-transplant patients with normoglycemia prior to transplantation. The 3-month and 1-, 3-, 5-, 10-, and 20-year cumulative incidence of hyperglycemia was 10.4%, 11.4%, 13.4%, 15.2%, 22.7%, 27.9%, and 38.3%, respectively. Among them, 61.6% of patients developed posttransplantation diabetes mellitus. The utility of tacrolimus was a risk factor
Table 3 The efficacy and safety of tacrolimus compared with cyclosporine

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<td>Yu et al(^{50})</td>
<td>90 cadaveric renal transplant recipients</td>
<td>Randomized into tacrolimus (n=40) and CsA (n=50) groups after cadaveric renal transplantation</td>
<td>Kidney transplantation</td>
<td>12 months</td>
<td>Tacrolimus had a better safety profile and efficacy and fewer side effects than CsA.</td>
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<td>Wang et al(^{55})</td>
<td>57 cadaveric renal transplant recipients</td>
<td>Randomized into tacrolimus (n=25) and CsA (n=32) groups after cadaveric renal transplantation</td>
<td>Kidney transplantation</td>
<td>Mean follow-up of 12.1 months (7–17 months)</td>
<td>Dramatic reduction in the incidence and severity of acute allograft rejection in patients treated with tacrolimus.</td>
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<td>Cheung et al(^{56})</td>
<td>76 patients received cadaveric kidneys from 38 donors</td>
<td>Each pair of kidneys was randomly assigned to a separate group and received triple-immunosuppressive therapy with either tacrolimus or Neoral CsA</td>
<td>Kidney transplantation</td>
<td>Mean follow-up duration was 6.1±1.8 years</td>
<td>Tacrolimus-based therapy provided adequate immunosuppression with better renal function and less acute rejection compared with CsA-based therapy.</td>
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<td>Ji et al(^{57})</td>
<td>31 patients with a histological diagnosis of CAN</td>
<td>Conversion from a CsA-based regimen to a tacrolimus-based regimen</td>
<td>Kidney transplantation</td>
<td>36 months</td>
<td>Conversion from a CsA-based regimen to a tacrolimus-based regimen was an effective choice for salvage of patients with abnormal graft renal function induced by CAN.</td>
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<td>Peng et al(^{58})</td>
<td>73 renal transplantation patients with CAN proved by allograft biopsy</td>
<td>Patients were either converted to tacrolimus (tacrolimus group, n=43) or remained on their initial CsA-based immunosuppression (CsA group, n=30)</td>
<td>Kidney transplantation</td>
<td>12 months</td>
<td>Conversion from CsA to tacrolimus was an effective and safe alternative therapy for delaying the progression of renal dysfunction induced by CAN.</td>
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<td>Liu et al(^{59})</td>
<td>109 recipients carrying HBV</td>
<td>Randomized into tacrolimus group (52 cases) and CsA group (57 cases) after kidney transplantation</td>
<td>Kidney transplantation</td>
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<td>For HBV-carrying renal transplant recipients, tacrolimus as the primary choice of immunosuppressant could be more effective and safer than CsA.</td>
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<td>Liu et al(^{60})</td>
<td>27 patients who developed DGF due to acute renal tubular cell necrosis</td>
<td>Randomized into tacrolimus (n=15) and CsA (n=12) groups after cadaveric renal transplantation</td>
<td>Kidney transplantation</td>
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<td>Tacrolimus-based triple-combined immunosuppressive regimen was the optimal combination of immunosuppressants in cadaveric renal transplant recipients experiencing DGF.</td>
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<td>Lo et al(^{61})</td>
<td>94 LTx performed in 92 patients</td>
<td>The results of 44 LTx performed after November 1996 using a double regimen of tacrolimus and steroids were compared with those of 50 LTx given a triple regimen of CsA, steroids, and azathioprine before this period</td>
<td>LTx</td>
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<td>Tacrolimus offered superior immunosuppression, and will replace CsA as the primary baseline drug in patients after LTx.</td>
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<td>Lo et al(^{4})</td>
<td>61 patients after orthotopic LTx</td>
<td>13 patients were converted from CsA to tacrolimus. 12 patients received a double regimen of primary tacrolimus-based immunosuppression</td>
<td>LTx</td>
<td>Median follow-up of 12 months (range 1–47 months)</td>
<td>Tacrolimus was highly effective as rescue therapy for resistant rejection, and primary therapy with tacrolimus resulted in a low rejection rate.</td>
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<td>Ye et al(^{62})</td>
<td>50 LTx patients</td>
<td>Tacrolimus high-concentration (20 patients), tacrolimus mid-concentration (20), CsA-tacrolimus (5), and tacrolimus-CsA (5) groups</td>
<td>LTx</td>
<td>12 months</td>
<td>Tacrolimus was a highly effective immunosuppressive agent, and the mid-concentration protocol was a better one.</td>
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**Abbreviations:** CAN, chronic allograft nephropathy; CsA, cyclosporine A; DGF, delayed graft function; HBV, hepatitis B Virus; LTx, liver transplantation(s).
for developing diabetes (relative risk 1.835, 95% confidence interval 1.181–2.851; \( P=0.007 \)). Ling et al\(^{64} \) analyzed data from 125 Chinese liver-transplant patients without a history of diabetes. Multivariate logistic regression analysis indicated that a serum tacrolimus concentration of more than 10 ng/mL 1 month after transplantation was an independent risk factor for predicting posttransplantation diabetes mellitus (odds ratio 3.264, \( P=0.017 \)). Therefore, serum glucose levels should be strictly monitored in organ-transplant patients. For patients with tacrolimus-associated diabetes, if the condition cannot be controlled by standard drug therapy, conversion to CsA should be considered. Tacrolimus is a calcineurin inhibitor with less nephrotoxicity compared to CsA. However, patients taking tacrolimus still have a risk of developing renal impairment. Lai et al\(^{65} \) conducted a study of 124 liver-transplant patients. Of these, 102 patients took tacrolimus as immunosuppressive drug and nine (8.8%) patients developed renal adverse effects. Calcineurin inhibitor-associated nephrotoxicity can be significantly reduced by decreasing the dose of tacrolimus and increasing the dose of MMF.

Tacrolimus has the potential to induce neurotoxicity, particularly when used in pediatric patients. Xie et al\(^{66} \) concluded their single-center clinical experience, and suggested that in pediatric transplant patients, tacrolimus-induced neurotoxicity is manifested by epilepsy that occurs within 2 weeks after transplant. High blood tacrolimus concentration can induce epileptic seizures; the adverse effects of tacrolimus are closely associated with blood concentrations.\(^{67} \)

Adverse effects always occur when blood tacrolimus concentrations are higher than the therapeutic concentration – 15 ng/mL. However, most adverse effects are transient, and resolve when the treatment is withdrawn. Therefore, the TDM of tacrolimus trough concentrations is necessary. Transplant recipients require long-term immunosuppressive treatment, along with long-term survival of the graft organ. Therefore, they have a higher risk of developing infections and cancers. Chen et al\(^{68} \) analyzed data from 1,806 renal transplant patients; 252 patients died, with 146 (57.9%) from infection and 10 (4.0%) from malignant tumors. Pneumonia is the most common of transplant-associated infections. Zhang et al\(^{69} \) reported in 386 kidney transplant patients who received tacrolimus-based immunosuppression an incidence of pneumonia of 7.25%, most of which occurred within 6 months after transplant. Infections were usually associated with tacrolimus overdose. In addition, the expressive status of CYP3A5 was also an independent risk factor for the development of infections in Chinese pediatric liver-transplant patients.\(^{69} \)

Combination therapy with steroids significantly affected infection and tumor-recurrence rates of transplant patients who received tacrolimus-based immunosuppressive therapy. In a study conducted by Hu et al\(^{72} \) a total of 502 liver-transplant recipients were divided into the following groups: tacrolimus with basiliximab induction and steroid-avoidance group, tacrolimus with 14 days of steroid-withdrawal group, tacrolimus with 3 months of steroid-withdrawal group, and tacrolimus with 6 months of steroid-withdrawal group. The incidence of HBV infection in these groups was 20.5%, 30.5%, 56.1%, and 62.2%, respectively. The 3-year HCC-recurrence rate was lowest in the basiliximab-induction group and the steroid-avoidance group (12.8%, \( P=0.037 \)). These results indicated that a basiliximab-induction and steroid-avoidance immunosuppressive protocol can reduce HBV infection and HCC recurrence after liver transplantation.

In the PRC, calcineurin inhibitors are widely used in combination with mycophenolic acid (MPA), an antimetabolite immunosuppressant. It is reported that tacrolimus can affect the metabolism of MPA. Therefore, the MPA concentration should also be monitored when combined with calcineurin inhibitors, in order to improve the safety of transplant recipients.\(^{70} \)

In spite of the potential adverse effects of tacrolimus, it is still the most important immunosuppressive agent for Chinese transplant patients, due to its high efficacy and low toxicity. Some strategies can be adopted to control transplant rejection effectively and to the maximum extent possible limit the toxicity of tacrolimus, including optimizing dosage and blood concentration, adopting appropriate combination regimens and personalizing regimens for each patient.

**Patient satisfaction and adherence**

The success of organ transplantation significantly improves quality of life in end-stage organ failure. However, patients confront certain challenges, such as economic burden and side effects, during the course of their lifetime. Psychological issues may also negatively influence treatment adherence. Approximately 20% of patients are unable to follow up, or cannot follow instructions to adjust drug dosage; some change or stop therapy on their own, resulting in adverse effects.\(^{71} \) Weng et al\(^{72} \) found that there was a significant difference in adherence between patients with once- or twice-daily dosage. The tacrolimus sustained-release capsule is administered only once daily, and its efficacy in preventing acute rejection is comparable with tacrolimus. There are no significant differences in the safety profiles between the formulations.\(^{73} \) The once-daily tacrolimus formulation can significantly improve patient adherence; however, in order to maintain a similar tacrolimus blood concentration, the once-daily dosage of tacrolimus should increase by 30%.\(^{74} \)
Special features

Since the genetic backgrounds of various ethnic groups are different, the gene variations that can affect the metabolism of tacrolimus are different in various ethnic groups. It has been reported that COMT rs2283273, COMT rs4646312, and POR*28 were associated with tacrolimus trough blood concentrations in American renal transplant patients. However, the association between these variants and tacrolimus trough concentration was not found in Chinese renal transplant recipients. There are reports that CYP3A4*22 can affect tacrolimus pharmacokinetics in European renal transplant patients, whereas CYP3A4*22 has not yet been found in Chinese renal transplant patients. CYP3A5 6986A>G (*1/*3) is a well-known genetic variation that can significantly affect the metabolism of tacrolimus. The gene frequency of this variant also varies with ethnic group. It was reported that the frequency of CYP3A5 expressers (CYP3A5*1/*1 and *1/*3) was 85% in African–Americans. In Asians, the frequency is 56%, and in Caucasians the frequency is about 16%. The variation of genetic background in different ethnic groups is a key factor leading to the different tacrolimus dosages used in Chinese and Western transplant recipients.

In Chinese adult liver-transplant patients, 78.47% have HBV, whereas HCV accounts for approximately 60% of liver transplants performed in the US. Due to the unprecedented proportion of patients with HBV-associated HCC, the application of the Milan criteria is limited in Chinese liver-transplant patients. Niu et al. found that HCC-recurrence rates at postoperative years 1, 2, 3, and 4 in the sirolimus group were 13.3%, 36.7%, 43.3%, and 53.3%, respectively, and were 38.7%, 67.7%, 74.2%, and 77.4%, respectively, in the tacrolimus group. Sirolimus significantly reduced tumor recurrence and increased survival for Chinese liver transplant recipients with HCC beyond Milan criteria. Based on this standard, tacrolimus is still a first-choice immunosuppressive agent for patients in the first month after liver transplantation. After the first postoperative month, sirolimus, which has antitumor effects, can be added to the immunosuppressive regimen and other immunosuppressive agents can be withdrawn gradually. Without decreasing postoperative or tumor-free survival, the Hangzhou criteria effectively expands the indication range for liver cancer-associated liver transplantation. Compared to the Milan criteria, the Hangzhou criteria increase the number of HCC patients who are eligible for liver transplantation by 37.5%. Therefore, more HCC patients can benefit from application of the Hangzhou criteria.

Conclusion

In summary, tacrolimus has been used in Chinese organ transplantation for over 10 years, and is the first-choice calcineurin inhibitor. The safety and efficacy of tacrolimus in preventing posttransplant acute rejection, as well as improving graft-organ survival, have been validated in many clinical trials. Personalized use of tacrolimus has gradually gained the attention of researchers. Owing to a narrow therapeutic range and large individual variability in its pharmacokinetics, the personalized use of tacrolimus is a challenge in clinical practice. To improve tacrolimus efficacy, reduce the incidence of side effects, and prolong graft survival, the appropriate initial and maintenance dose of tacrolimus, rational combination of tacrolimus with other agents, and optimization of immunosuppressive regimens are very important. We should evaluate patients’ immune status according to genetic background, liver function, nutritional state, complications such as infection and cancer, and TDM, to find the optimal balance between efficacy and adverse effects, and to personalize the initial and maintenance dose of tacrolimus further for Chinese patients. Conversion from a general therapy regimen for all patients to personalized regimens is the upcoming trend for tacrolimus use in Chinese organ transplantation.

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Disclosure

The authors report no conflicts of interest in this work.

References


Optimizing use of tacrolimus in People’s Republic of China