



Отчет подобия

Метаданные

Название организации

National Scientific Center of Surgery named after A.N. Syzganov

Название

GENETIC DETERMINANTS OF TACROLIMUS METABOLISM ASSOCIATED WITH CYP3A5 IN KIDNEY TRANSPLANTATION: A LITERATURE REVIEW

Автор

Aigul Aubakirova

Подразделение

National Scientific Center of Surgery named after A.N. Syzganov

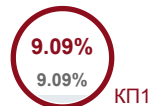
Тревога

В этом разделе вы найдете информацию, касающуюся текстовых искажений. Эти искажения в тексте могут говорить о ВОЗМОЖНЫХ манипуляциях в тексте. Искажения в тексте могут носить преднамеренный характер, но чаще, характер технических ошибок при конвертации документа и его сохранении, поэтому мы рекомендуем вам подходить к анализу этого модуля со всей долей ответственности. В случае возникновения вопросов, просим обращаться в нашу службу поддержки.

Замена букв		0
Интервалы		0
Микропробелы		0
Белые знаки		0
Парафразы (SmartMarks)		32

Объем найденных подобиий

КП-ия определяют, какой процент текста по отношению к общему объему текста был найден в различных источниках.. Обратите внимание!Высокие значения коэффициентов не означают плагиат. Отчет должен быть проанализирован экспертом.


25

Длина фразы для коэффициента подобия 2

6049

Количество слов

39467

Количество символов

Подобия по списку источников

Ниже представлен список источников. В этом списке представлены источники из различных баз данных. Цвет текста означает в каком источнике он был найден. Эти источники и значения Коэффициента Подобия не отражают прямого плагиата. Необходимо открыть каждый источник и проанализировать содержание и правильность оформления источника.

10 самых длинных фраз

Цвет текста

ПОРЯДКОВЫЙ НОМЕР	НАЗВАНИЕ И АДРЕС ИСТОЧНИКА URL (НАЗВАНИЕ БАЗЫ)	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)	Цвет текста
1	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846312/	44	0.73 %
2	Influence of Genetic Polymorphisms in CYP3A5, CYP3A4, and MDR1 on Tacrolimus Metabolism after kidney transplantation Lyazzat Nazarova, Aida Zhenissova, Sholpan Altynova, Malika Sapargalievya, Dias Malik, Aizhan Abdikadirova, Mels Assykbayev, Mirgul Bayanova, Aidos Bolatov, Saitkarim Abdugafarov, Yuriy Pya;	24	0.40 %

3	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5836651/	17 0.28 %
4	Re_ Meta_ Papillo 2/14/2025 National Scientific Center of Surgery named after A.N. Syzganov (National Scientific Center of Surgery named after A.N. Syzganov)	16 0.26 %
5	THE ROLE OF INTERLEUKINS IN THE PATHOGENESIS OF ATRIAL FIBRILLATION LITERATURE REVIEW 1/6/2025 National Scientific Center of Surgery named after A.N. Syzganov (National Scientific Center of Surgery named after A.N. Syzganov)	14 0.23 %
6	https://cyberleninka.ru/article/n/impact-of-cyp3a5-gene-polymorphism-on-tacrolimus-pharmacokinetics-in-kidney-transplant-patients	13 0.21 %
7	https://cyberleninka.ru/article/n/impact-of-cyp3a5-gene-polymorphism-on-tacrolimus-pharmacokinetics-in-kidney-transplant-patients	11 0.18 %
8	THE ROLE OF INTERLEUKINS IN THE PATHOGENESIS OF ATRIAL FIBRILLATION LITERATURE REVIEW 1/6/2025 National Scientific Center of Surgery named after A.N. Syzganov (National Scientific Center of Surgery named after A.N. Syzganov)	11 0.18 %
9	https://cyberleninka.ru/article/n/impact-of-cyp3a5-gene-polymorphism-on-tacrolimus-pharmacokinetics-in-kidney-transplant-patients	11 0.18 %
10	https://cyberleninka.ru/article/n/impact-of-cyp3a5-gene-polymorphism-on-tacrolimus-pharmacokinetics-in-kidney-transplant-patients	11 0.18 %

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ПОРЯДКОВЫЙ НОМЕР	НАЗВАНИЕ	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)
Источник: Paperity		
1	Influence of Genetic Polymorphisms in CYP3A5, CYP3A4, and MDR1 on Tacrolimus Metabolism after kidney transplantation Lyazzat Nazarova, Aida Zhenissova, Sholpan Altynova, Malika Sapargalievya, Dias Malik, Aizhan Abdikadirova, Mels Assykbayev, Mirgul Bayanova, Aidos Bolatov, Saitkarim Abdugafarov, Yuriy Pya;	34 (2) 0.56 %
2	Clinical implementation of pharmacogenetics in kidney transplantation: calcineurin inhibitors in the starting blocks. van Gelder T., N. Shuker, R. Bouamar, D. Hesselink, L. Elens, van Schaik R.;	24 (4) 0.40 %
3	Effects of CYP3A4*22 and POR*28 variations on the pharmacokinetics of tacrolimus in renal transplant recipients: a meta-analysis of 18 observational studies Li, Xingang, Li, Zhe, Cheng, Sheng, Li, Dandan, Guo, Heng, Dong, Yiwen, Wang, Xiaozhen, Zheng, Yingming, Li, Ze;	18 (3) 0.30 %
4	CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment Yingjie Cao;	16 (3) 0.26 %
5	Evaluation of IL-2 and Dexamethasone intracavitary injection on the management of malignant effusion in children with solid tumors or lymphoma Zhang, Yu-Tong, Chang, Jian, Zhong, Xiao-dan, Gao, Yan-li;	9 (1) 0.15 %
6	The Impact of Single Nucleotide Polymorphisms on the Pharmacokinetics of Tacrolimus in Kidney Allograft Recipients of Northern-West, Iran Ali Mousavi, Sepideh Zununi Vahed, Mohammadreza Ardalan, Seyyedeh Mina Hejazian, Samaneh Esfahanian, Mehdi Haghj, Elaheh Jabbari Hagh, Elham Ahmadian;	6 (1) 0.10 %

7	Dosing equation for tacrolimus using genetic variants and clinical factors. A. Birnbaum, C. Passey, P. Jacobson, A. Israni, R. Brundage, W. Oetting;	6 (1) 0.10 %
8	A systematic review and meta-analysis recite the efficacy of Tacrolimus treatment in renal transplant patients in association with genetic variants of CYP3A5 gene. P. Chauhan, R. Srivastava, N. Solanki, N. Shete, A. Konnur, R. Hemani, S. Gang, S. Pandey;	6 (1) 0.10 %
9	Whole exome sequencing for the identification of CYP3A7 variants associated with tacrolimus concentrations in kidney transplant patients Hun Soon Jung, Yon Su Kim, Myeong Gyu Kim, Minji Sohn, Young Kee Shin, Jung Mi Oh, Eun Young Song, Jongwon Ha, Sang-II Min, Jungsoo Gim, Nayoung Han, In-Wha Kim;	5 (1) 0.08 %
10	Tacrolimus Dose-Conversion Ratios Based on Switching of Formulations for Patients with Solid Organ Transplants. V. Leclerc, W. Kuan, B. Drolet, N. Châteauevert;	5 (1) 0.08 %
11	Risk factors for calcineurin inhibitor nephrotoxicity after renal transplantation: a systematic review and meta-analysis Chen W, Wen Y, Xia T, Gao S, Zhu S, Tao X, Zhang F, Li M;	5 (1) 0.08 %

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ПОРЯДКОВЫЙ НОМЕР	НАЗВАНИЕ	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)
1	THE ROLE OF INTERLEUKINS IN THE PATHOGENESIS OF ATRIAL FIBRILLATION LITERATURE REVIEW 1/6/2025 National Scientific Center of Surgery named after A.N. Syzganov (National Scientific Center of Surgery named after A.N. Syzganov)	35 (3) 0.58 %
2	Re_ Meta_ Papillo 2/14/2025 National Scientific Center of Surgery named after A.N. Syzganov (National Scientific Center of Surgery named after A.N. Syzganov)	16 (1) 0.26 %

из программы обмена базами данных (0.17 %)

ПОРЯДКОВЫЙ НОМЕР	НАЗВАНИЕ	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)
1	Final exam Balzhan.docx 4/25/2024 University of International Business (UIB) (University of International Business)	10 (1) 0.17 %

из интернета (5.87 %)

ПОРЯДКОВЫЙ НОМЕР	ИСТОЧНИК URL	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)
1	https://cyberleninka.ru/article/n/impact-of-cyp3a5-gene-polymorphism-on-tacrolimus-pharmacokinetics-in-kidney-transplant-patients	90 (10) 1.49 %
2	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5846312/	90 (7) 1.49 %
3	https://repub.eur.nl/pub/93008/160629_Shuker-Nauras-M.pdf	45 (8) 0.74 %
4	http://www.science.gov/topicpages/c/cyp3a4+cyp3a5+cyp3a7.html	25 (3) 0.41 %
5	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5836651/	17 (1) 0.28 %
6	https://cyberleninka.ru/article/n/genetic-polymorphism-of-cyp3a5-as-a-key-regulator-of-pharmacokinetics-of-tacrolimus-in-kidney-transplant-patients-evidence-in	16 (2) 0.26 %

7	https://library.poltekkesdepkes-sby.ac.id/public/Gizi/2023-3.The%2014th%20European%20Nutrition%20Conference%20FENS.pdf	15 (2) 0.25 %
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10	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819215/	11 (1) 0.18 %
11	https://www.wjnet.com/2220-3230/CitedArticlesInF6?id=10.2217%2Fpgs.13.199	9 (1) 0.15 %
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Список принятых фрагментов (нет принятых фрагментов)

ПОРЯДКОВЫЙ НОМЕР	СОДЕРЖАНИЕ	КОЛИЧЕСТВО ИДЕНТИЧНЫХ СЛОВ (ФРАГМЕНТОВ)
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Conflict of interest The authors declare that there is no conflict of interest in this work.

LITERATURE REVIEW

GENETIC DETERMINANTS OF TACROLIMUS METABOLISM ASSOCIATED WITH CYP3A5 IN KIDNEY TRANSPLANTATION: A LITERATURE REVIEW

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Annotation

Background Kidney transplantation is the most effective treatment for end-stage chronic kidney disease, improving quality of life and reducing mortality compared to dialysis. Transplant success depends on HLA compatibility, immune sensitization, immune status, and immunosuppressive therapy.

Tacrolimus, a key immunosuppressant, prevents graft rejection by suppressing T-cell activity and **is metabolized by CYP3A 4 and CYP3A5 enzymes. CYP3A5** gene polymorphisms influence enzyme activity and tacrolimus metabolism.

Methods The review analyzed 46 out of 141 publications from PubMed, MEDLINE, Embase, Scopus, and Cochrane Library databases that met inclusion criteria and focused on the **role of CYP3A5** gene polymorphisms in tacrolimus metabolism in kidney transplant patients.

Results **CYP3A5 gene** polymorphisms significantly affect tacrolimus pharmacokinetics. **Carriers of the *1 allele** (expressers) demonstrated accelerated metabolism requiring higher doses, while **patients with the *3/*3 genotype** (non-expressers) exhibited slower metabolism, allowing for reduced doses but increasing the risk of toxicity, including nephrotoxicity. An analysis of 46 publications and randomized studies confirmed that CYP3A5 genotyping enables personalized tacrolimus dosing. For expressers, genotyping facilitated faster achievement of therapeutic concentrations, while for non-expressers, it reduced the risk of toxic effects. However, long-term differences in clinical outcomes between groups with and without genotyping remain statistically insignificant, emphasizing the need for larger-scale studies to validate this approach's efficacy.

Conclusion CYP3A5 polymorphisms play a key role in personalizing immunosuppressive therapy. Genotyping optimizes tacrolimus dosing, reducing rejection and toxicity risks. Integrating pharmacogenetic testing into clinical practice could improve transplantation outcomes.

Keywords: tacrolimus, CYP3A5 gene, kidney transplantation, immunosuppression, genotyping.

Introduction

Between 2012 and 2023, 2,475 organ transplants were performed in Kazakhstan, of which 1,833 were kidney transplants. This method is the most effective treatment for end-stage chronic kidney disease, improving quality of life and reducing mortality compared to dialysis.¹ The success of transplantation depends on HLA compatibility between donor and recipient, the level of immune sensitization, and the selection of immunosuppressive therapy to prevent graft rejection. A personalized approach to treatment, including therapy optimization and dynamic follow-up, improves long-term outcomes.^{2,3}

Tacrolimus is a key immunosuppressive agent that prevents acute and chronic rejection of transplanted organs. This calcineurin inhibitor suppresses T-cell activity, reducing immune response. It is metabolized by **CYP3A4 and CYP3A5** enzymes, the expression of which is determined by genetic variations **in the CYP3A5 gene**.^{4,5} **The primary polymorphisms of CYP3A5 (*1 and *3)** determine differences in tacrolimus metabolism. **Carriers of the *1 allele** ("expressors") exhibit accelerated metabolism, requiring higher doses, while carriers of the *3/*3 genotype ("non-expressors") have slower metabolism, allowing dose reductions but increasing the risk of toxicity.⁶

Genotyping CYP3A5 enables individualized tacrolimus dosing, reducing the risk of rejection and side effects. Adjusting therapy based on pharmacogenetic testing improves the safety and efficacy of transplantation.⁷

Objective: To analyze current data on the **impact of CYP3A5 gene polymorphisms on tacrolimus pharmacokinetics and efficacy in** kidney transplantation.

Materials and Methods

This review analyzed 46 of 141 publications from PubMed, MEDLINE, Embase, Scopus, and Cochrane Library databases, focusing on the role of **CYP3A5 gene polymorphisms in tacrolimus metabolism among kidney transplant** recipients. Keywords used included "CYP3A5," "tacrolimus," "pharmacokinetics," "kidney transplantation," "immunosuppression," and "genetic polymorphisms."

Inclusion criteria: Studies addressing CYP3A5 polymorphisms and their association with tacrolimus dosing and effects, **published in peer-reviewed journals within the last 10 years**.

Exclusion criteria: Studies without data on CYP3A5, unrelated to transplantation, or published over 10 years ago.

The analysis followed PRISMA guidelines, focusing on the **effects of CYP3A 5** on metabolism, clearance, tacrolimus concentration, and clinical outcomes such as rejection and toxicity.

Ethical approval. **This study did not involve** human participants or personal clinical data. However, it **was reviewed and approved by the Ethics Committee of the JSC "National Scientific Center of Surgery named after A.N. Syzganov,"** Almaty, Kazakhstan (Protocol No. 1, dated 24.02.2025).

Results

The introduction of calcineurin inhibitors such as cyclosporine (CsA) and tacrolimus (Tac) marked a significant milestone in transplantation, greatly improving patient and graft survival. CsA, derived from the fungus *Tolypocladium inflatum* and first used by Sir Roy Calne in 1987, reduced the rate of acute rejection to 15% and increased the one-year survival rate of kidney transplant recipients to 85%.^{8,9} Its success became the foundation for its use in liver, heart, and other organ transplantation.

CsA acts by binding to cyclophilin, inhibiting calcineurin, and preventing T-cell activation, thereby reducing immune response and lowering the risk of graft rejection.⁹ Tacrolimus, a macrolide, was identified in the 1990s from the bacterium *Streptomyces tsukubaensis*. Its clinical use began with liver transplantation under the guidance of Thomas Starzl, after which Tac became widely adopted in kidney, heart, and lung transplantation.¹⁰ Tac has shown superior efficacy compared to CsA, making it a cornerstone of modern immunosuppressive protocols.

Unlike CsA, Tac binds to FK506-binding protein, which also interacts with calcineurin. Similar to CsA, Tac blocks calcineurin, preventing **Nuclear factor of activated T-cells (NFAT) translocation to the nucleus and** inhibiting the expression of cytokines such as interleukin-2 (IL-2). However, Tac has several advantages, including higher efficacy at lower doses, reduced risk of toxic effects, induction of apoptosis in antigen-specific activated T cells, suppression of IL-10 production (reducing antibody production by B cells), and inhibition of TGF- β , which prevents fibrosis in kidney transplants.^{11,12} Despite similarities to CsA, Tac has a more favorable safety profile, including a lower risk of fibrosis and the ability to be used at lower doses.¹³ Consequently, the international Kidney Disease: Improving Global Outcomes (KDIGO) guidelines in 2009 recommended Tac as the first-line agent for initial and maintenance immunosuppressive therapy after kidney transplantation.^{14,15}

Comparative studies between CsA and Tac in transplantation are well-documented in the literature. An analysis of data from PubMed, Cochrane Collaboration Resources, and Google Scholar since 2005 identified four **meta-analyses of randomized controlled trials (RCTs) evaluating the efficacy and safety of** these drugs.^{16,17,18} Key primary outcomes included acute rejection rates and graft loss, while secondary outcomes encompassed insulin-dependent diabetes mellitus (IDDM), nephropathy, hypercholesterolemia, and hypertension.¹⁸ Tac demonstrated significant advantages over CsA, including lower acute rejection rates and improved long-term graft survival. However, Tac was more frequently associated with IDDM due to its impact on pancreatic β -cells, while the incidence of nephropathy and hypertension was similar for both drugs.^{19,20,21}

Tacrolimus, a lipophilic macrolide, is **metabolized by CYP3A 4 and CYP3A5** enzymes, leading to substantial **individual variability in its pharmacokinetics**.²² Tacrolimus bioavailability ranges from 10% to 40%, depending on CYP3A activity. CYP3A5¹ carriers (expressors) require higher doses due to accelerated metabolism, while CYP3A5³ carriers (non-expressors) have slower metabolism, increasing the risk of toxicity,^{23,24} with a prolonged half-life (12-24 hours), Tac can be administered once or twice daily, facilitating treatment adherence.²⁵ Tac inhibits calcineurin, preventing NFAT activation and IL-2 transcription, ensuring robust immunosuppressive effects and reducing graft rejection risks.^{25,26}

Tac also inhibits TGF- β , preventing fibrosis, induces apoptosis in activated T cells, and suppresses IL-10 production, reducing B-cell activation and humoral rejection risks.^{27,28} However, its narrow therapeutic window necessitates regular monitoring to minimize adverse effects.²⁹ Common side effects of Tac include diabetes mellitus (due to effects on pancreatic β -cells), nephrotoxicity, and hypertension, which require careful management.^{22,30}

Tacrolimus is a critical immunosuppressive drug in transplantation medicine for preventing organ rejection. Its pharmacokinetics are characterized by low and highly variable bioavailability, complicating therapy individualization. Tacrolimus bioavailability ranges from 5% to 90%, with an average of approximately 25%.^{23,31,32} This variability is driven by absorption characteristics in the gastrointestinal tract and **extensive metabolism by the cytochrome P450** system. Tac is predominantly **metabolized by CYP3A 5** and CYP3A4, with minor contributions from CYP3A 7 and CYP3A 43, which are expressed in organs such as the small intestine, liver, and kidneys.^{33,34} The small intestine plays a crucial role in the presystemic biotransformation of Tac, while the liver is the primary site of systemic metabolism, which regulates its pharmacokinetics.³⁵

Once in systemic circulation, approximately 99% of Tac binds **to erythrocytes, resulting in whole blood concentrations** 10-30 times higher than plasma levels. For its immunosuppressive action, Tac must be in a free, dissociated form, highlighting the importance of factors influencing its

metabolism, distribution, and lymphatic penetration.³⁶ CYP3A5 enzymes in the kidneys can limit Tac accumulation in tissues, leading to discrepancies between blood and tissue concentrations, potentially reducing efficacy and increasing toxicity risks.^{37,38} Drug interactions and genetic variations in CYP3A expression further impact Tac bioavailability. CYP3A5 polymorphisms significantly contribute to pharmacokinetic variability and efficacy among different ethnic groups.³⁹ These challenges complicate achieving stable therapeutic Tac concentrations, increasing the risk of graft rejection or adverse effects. Optimizing therapy requires consideration of key determinants of Tac bioavailability, metabolism, and distribution. A deeper understanding of Tac pharmacodynamics, pharmacokinetics, and pharmacogenetics will enable personalized treatment approaches, crucial for transplant patients.^{40,41}

Multiple factors influence Tac nephrotoxicity risk, including donor age, donor sex (males are more susceptible), **recipient age, recipient body mass index, cold ischemia time, HLA mismatching, donor hypertension, recipient atherosclerosis, diabetes, and infectious complications.** **Recipient CYP3A5 genotype, particularly the *3/*3 allele,** is also a significant risk factor.^{23,42} **A meta-analysis of 12** prospective studies by Xia T et al. identified donor age, recipient atherosclerosis, and the **CYP3A5 *3/*3 genotype** as key risk factors for acute Tac nephrotoxicity.^{43,44}

The CYP3A5 gene, which encodes its eponymous enzyme, has two primary alleles: *1 and *3. **Patients with the homozygous CYP3A5 *3/*3 genotype** lack functional enzyme activity, leading to slower Tac metabolism and lower dose requirements. Conversely, carriers of the *1/*1 or *1/*3 alleles exhibit higher enzyme expression, necessitating higher Tac doses to achieve therapeutic levels. On average, expressors require 50% higher doses than non-expressors, emphasizing the importance of genotyping for individualized Tac dosing. However, genotyping is rarely used in routine clinical practice, with Tac doses typically adjusted based on body weight and therapeutic drug monitoring.^{24,26} Two randomized studies explored the use of genotyping for tacrolimus dosing optimization. The findings indicate that genotype distribution (Table 1) influences dose requirements, with expressors needing higher doses than non-expressors.

Despite **the evident impact of CYP3A5 genotype on** Tac dosing, the feasibility of pre-transplant genotyping in clinical practice remains under evaluation. Pre-transplant genotyping could help calculate optimal doses in advance, particularly **in the early post-transplant period** when rejection and toxicity risks are highest.⁴⁵⁻⁴⁷

Table 1. **Frequency of CYP3A5 alleles in different ethnic populations**

Ethnic population	CYP3A5 *1/*1 (%)	CYP3A5 *1/*3 (%)	CYP3A5 *3/*3 (%)
Caucasian	46.48	11.13-17.82-86	Black 49.50
Indian	51-53	2.5-11 38-57 32-60	Chinese 33.44
		7.7	44.8 47.4

Two randomized studies investigated the potential use of genotyping to optimize Tac dosing. The first study, conducted in France (n=280),⁵⁴ included patients whose Tac doses were calculated based on body weight (0.20 mg/kg) and genotype (expressors received 0.30 mg/kg, while non-expressors received 0.15 mg/kg). The second study, conducted in the Netherlands (n=240),²⁹ employed a similar design but differed in the timing of therapy initiation. In the French study, Tac therapy started on the seventh day, allowing patients with genotyping to achieve target drug concentrations (10-15 ng/mL) more quickly. The Dutch study found **no statistically significant differences between the groups** but confirmed **the influence of the CYP3A5 genotype on** Tac dose dependence.^{41,55}

These studies underscore the need for further research to evaluate the clinical utility of genotyping. Larger and more prolonged randomized studies are required to assess the feasibility of implementing pre-transplant genotyping and its impact on transplant therapy outcomes.¹⁸

Discussion

The discovery and development of calcineurin inhibitors, such as cyclosporine and tacrolimus, have profoundly impacted the field of transplantation, significantly improving recipient and graft survival rates. Tacrolimus, with its unique properties, has become a cornerstone of modern immunosuppressive protocols, underscoring its clinical relevance in organ transplantation.^{24,56}

The side effects and interindividual variability in the pharmacokinetics and pharmacodynamics of tacrolimus highlight the need for personalized treatment approaches. Pharmacogenetic studies, particularly those evaluating CYP3A5 polymorphisms, play a crucial role in optimizing tacrolimus dosing.

Personalization of immunosuppressive therapy, combined with regular drug concentration monitoring, is key to minimizing complications and improving long-term outcomes for organ transplant patients.^{34,56}

The CYP3A5 gene, which encodes a protein belonging to the cytochrome P450 superfamily, plays a critical role in the metabolism of drugs, including tacrolimus, as well as in the synthesis of steroid hormones and other lipids. Cytochrome P450 proteins are monooxygenases that catalyze oxidation reactions essential for drug biotransformation, cholesterol synthesis, and the metabolism of steroids and vitamins. **The CYP3A5 gene** is located on chromosome 7q21.1 and is part **of a cytochrome P450 gene** cluster, which includes two pseudogenes. The **expression of CYP3A5** varies among populations and is regulated by single-nucleotide polymorphisms (SNPs), which can affect drug metabolism efficiency and predisposition to conditions such as hypertension.^{19,31}

In the context of tacrolimus metabolism, **CYP3A5 plays a** central role in the biotransformation of the drug, determining its pharmacokinetic parameters. Tacrolimus, widely used as an immunosuppressive agent to prevent graft rejection, presents challenges in dose individualization due to its low and variable bioavailability. The CYP3A5 protein catalyzes the hydroxylation of carbon-hydrogen bonds and participates in the presystemic biotransformation of tacrolimus, leading to its extensive first-pass metabolism in the small intestine and liver. Additionally, this enzyme facilitates the oxidative conversion of xenobiotics, such as tacrolimus and cyclosporine, affecting their pharmacokinetics.^{46,57}

The CYP3A5 gene has two main alleles, *1 and *3, which influence the enzyme's expression level. Patients with the *3/*3 genotype (non-expressors) exhibit significantly reduced CYP3A5 activity, leading to slower tacrolimus metabolism and a lower dose requirement. Conversely, carriers of the *1 allele (heterozygotes or homozygotes) show higher enzyme expression, resulting in faster tacrolimus metabolism and the need for higher doses to achieve therapeutic levels. Thus, genetic differences in CYP3A5 are a critical determinant of interindividual variability in tacrolimus pharmacokinetics.^{24,31} **The functional activity of CYP3A5 is essential, not** only for tacrolimus metabolism but also for the conversion of steroid hormones, such as testosterone and progesterone, as well as the synthesis of catecholestrogens and retinoic acid. The high catalytic activity of CYP3A5 enables it to metabolize 17 β -estradiol and estrone, along with xenobiotics such as nifedipine. For tacrolimus, CYP3A5 catalyzes its hydroxylation, resulting in metabolites that limit the drug's bioavailability. Furthermore, CYP3A5 contributes to the oxidative clearance of tacrolimus, which is particularly important for hepatic and renal clearance in post-transplant patients.^{27,47}

CYP3A5 expression is regulated by SNPs, which can influence tacrolimus metabolism and the efficacy and toxicity of other drugs. These genetic variations may also dictate the body's response to tacrolimus therapy, emphasizing the importance of considering pharmacogenetic data when personalizing treatment. Given the significance of CYP3A5 in tacrolimus metabolism, implementing pre-transplant genotyping could facilitate more precise dose adjustments, reducing toxicity risk and enhancing therapeutic efficacy.^{42,55}

In conclusion, **the CYP3A5 gene** and its polymorphisms are pivotal factors influencing the pharmacokinetic properties of tacrolimus, including its metabolism, bioavailability, and individual dose requirements. This makes CYP3A5 a key target for research in personalized transplantation medicine.

Limitations The included studies primarily analyzed the impact of CYP3A5 gene polymorphism in specific ethnic groups, which may limit the generalizability of the results to other populations. The studies employed different methodological approaches, complicating direct comparative analysis. The literature highlights a lack of long-term clinical studies evaluating the **impact of CYP3A5** genotyping on transplantation outcomes. The study suggests that other genetic factors and comorbidities, which were not accounted for in all studies, may influence the pharmacokinetics of tacrolimus. Different immunosuppressive therapy regimens may affect tacrolimus metabolism, necessitating further investigation.

What's known? Tacrolimus is a key component of immunosuppressive therapy in kidney transplant patients, prognosing both acute and chronic graft rejection. Tacrolimus metabolism is carried out by **the CYP3A4 and CYP3A5** enzymes. Patients who **carriers of the CYP3A5*1 allele** expressers have accelerated tacrolimus metabolism and require higher doses, whereas patients with the *3/*3 genotype non-expressers have slower metabolism, leading to increased drug concentrations in the blood and a higher risk of nephrotoxicity.

What's new? CYP3A5 genotyping is considered a potential tool for individualized tacrolimus dosing; however, its widespread clinical implementation remains limited.

Conclusion

Kidney transplantation in Kazakhstan is a vital area of medical care that significantly improves the quality of life for patients with end-stage chronic kidney failure. Immunosuppression using tacrolimus plays a key role in preventing graft rejection; however, its pharmacokinetic variability requires a meticulous approach to dosage selection. Genetic factors, such as the polymorphism of the CYP3A5 gene, significantly influence the metabolism and bioavailability of tacrolimus, underscoring the importance of incorporating genotyping into clinical practice. Pre-transplant genotyping can facilitate individualized therapy, reducing the risk of toxicity and rejection, while enhancing treatment efficacy.

It is anticipated that further scientific **research in this area will contribute to the development of** more accurate and accessible genotyping algorithms, strengthening the scientific and practical foundation of transplantology in Kazakhstan. Integrating these approaches into routine clinical practice will be a significant step toward personalized medicine, enabling consideration of individual patient characteristics and minimizing post-transplant complications.

Our literature review highlights the necessity of further investigating the role of genetic factors, including CYP3A5 gene polymorphism, in tacrolimus metabolism. These studies will not only deepen the understanding of the pharmacogenetics of the drug but also help design more effective treatment strategies, ultimately reducing the incidence of complications and extending the functional lifespan of the graft in patients in Kazakhstan.

Tacrolimus, due to its unique pharmacological properties, remains the first-line drug in modern transplantology. However, its use requires careful monitoring, study of pharmacogenetic factors, and an individualized approach to treatment, enabling the minimization of side effects and enhancement of immunosuppressive therapy efficacy.

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