International Immunopharmacology 57 (2018) 18–24

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Donor and recipient P450 gene polymorphisms influence individual pharmacological effects of tacrolimus in Chinese liver transplantation patients

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ARTICLE INFO

Keywords:
Liver transplantation
Tacrolimus
P450
SNP
Pharmacogenomics

ABSTRACT

The immunosuppressant drug tacrolimus (Tac) used for the prevention of immunological rejection is a metabolic substrate of cytochrome P450 enzymes. This study was designed to evaluate the short-term and long-term potential influence of single-nucleotide polymorphisms (SNPs) in CYP450 genes of liver transplant (LT) recipients as well as the donors on individual pharmacological effects of Tac and to guide individualized-medication from the perspective of pharmacogenomics. Twenty-one SNPs of the CYP450 gene were genotyped for both recipients and donors in 373 LT patients receiving Tac-based immunosuppressants. The Tac concentration/dosage ratio (C/D) was evaluated from the initial medication until one year after LT. The C/D ratio was significantly higher when the donor and/or recipient genotype of CYP3A5 rs776746 was G/G or rs15524 was T/T or rs4646450 was C/C all through one year after transplantation. Comparing the effect of donor gene variants of rs776746, rs15524, and rs4646450 on Tac C/D ratios with the recipients, statistically significant differences were found between the donor T/T group and the recipient T/T group in rs15524 at 1 month and 6 months, and at 6 months, the donor C/C group differed from the recipient C/C group in rs4646450. In conclusion, rs776746, rs15524, and rs4646450 of CYP3A5 had a significant influence on Tac pharmacological effects for both the initial use and long-term use. The donor liver genotype and the recipient intestine genotype contribute almost equally in the short-term, but the donor genotype had a greater effect than the recipient genotype at 6 months. Personalized Tac treatment after LT should be based on the CYP3A5 genotype.

1. Introduction

Liver transplantation has been considered as the only effective treatment for end-stage liver diseases, while the survival of graft recipients largely depends on the introduction of calcineurin inhibitors (CNIs), especially tacrolimus (Tac) in the 1990s [1,2]. However, Tac has a narrow therapeutic window and shows considerable interindividual and intraindividual pharmacokinetic variability. High Tac levels are prone to neurotoxicity, nephrotoxicity, infection and malignancy in the long term, while at subtherapeutic drug concentrations patients are prone to rejection. Hence, the success of the transplantation depends on a delicate balance between therapeutic efficacy and the side effects. Therapeutic drug monitoring (TDM) is recommended to maintain adequate levels of blood Tac [3]. However, TDM has some limitations and there has been no critical dosage regimen for Tac therapy, especially the initial dosage. Because different recipients respond differently to similar drug concentrations, reaching the target concentration may not ensure the safety of the drug or avoid the occurrence of immune rejection. Additionally, TDM is routinely performed after liver transplantation, not pre-transplantation, so it cannot predict the proper dose requirements or the initial dosage.

Based on the needs of an individualized treatment regimen, pharmacogenomics holds the potential to elucidate the inherited highly variable pharmacokinetics of Tac. Since Tac is mainly metabolized by the expression of cytochrome P450 isoenzymes (CYP450s) in various human organs and tissues, especially in the liver [4,5]. For liver

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https://doi.org/10.1016/j.intimp.2018.02.005
Received 25 September 2017; Received in revised form 8 February 2018; Accepted 9 February 2018

Table 1
Primers for each SNP.

Genetic variants		Primers
CYP2B6	rs2279343(A > G)	F:CCTCCCCTCCCTTCCCT
		R:CCGTGAAACCCTGGACC
	rs37452749(G > T)	F:CGTTTTCCAAAGACGATGGAGCA
		R:GGGCCCTCATGGACCC
CYP2C8	rs10509681(C > T)	F:TGGCCAGGGTCAAAGATATTTGGA
		R:TTCCAGGGCACAACCATAATG
CYP2C9	rs1799853(C > T)	F:GGTCACCCACCCTTGGTTTT
		R:CGCTGCGGAATTTTGGGAT
	rs1057910(A > C)	F:GCTGGTGGGGAGAAGGTCAA
		R:GCAAGACAGGAGCCACAT
	rs1057911(A > T)	F:TGGTAGAAGGGCGGCACA
		R:GGTTGACCCAAAGAACCTTGAC
	rs9332093(C > G)	F:AGTTTCATGAGTCAGGGACCAAGT
		R:AGGTCAGAAGAGTTTGGTTTTATAACAT
	rs9332098(A > G)	F:GGGAAACAGCACCAGAGATGC
		R:CCCTCAGTTACACTGAGCGT
CYP3A4	rs35599367(C > T)	F:AGTGATGCAGCTGGCCCTA
		R:GGGCTCCTTGATCTCAGAGG
	rs28371759(C > T)	F:GATTGGGCCACGAGCTCC
		R:GCCCTACATTGATCTGATTTACCT
	rs2740574(A > G)	F:ACTCAAGTGGAGCCATTGGCA
		R:TCAAGTATTTTGGAATGAGGACAGC
	rs36231115(A > G)	F:CACACCACTCACTGACCTCCT
		R:CCAATGGCTCCACTTGAGTTTC
	rs4646437(C > T)	F:GGGCTGCTGATCTCACTGCT
		R:CCCCTCTTTCAGGCCAGT
CYP3A5	rs776746(A > G)	F:CTAACCATAATCTCTTTAAAGAGCTCTTTTGTCTTTC
		R:CAAGGCTTCATATGATGAAGGGTAA
	rs10264272(C > T)	F:AGAGAAATAATGGATCTAAGAAACCAAATTTTAGGAACT
		R:GACTCTCTCAACAATCCACAAGA
	rs15524(C > T)	F:GGCACAGCTTTCTTGAAGACCA
		R:GTGGATTCAAGAGATGGAACCC
	rs4646450(C > T)	F:AGCGAGAGGACGCTATTGCA
		R:CTCTGCCTTGTCCAGAATACAC
	rs3800959(C > T)	F:ACCCTAAAAAACAAAAATTATGGATGAAGGAAGATT
		R:TGCTTCGCTATTTGCCTCAAC
	rs28365083(A > C)	F:CCTCAGGCTCTGTCCAGTACTT
		R:GGGTATTCATTCCCAAAGGGT
	rs28383472(A > G)	F:GAGAAAGAAATAATAGCCCACATACTTATTGAGAGA
		R:CCCCTTTGTGGAGAGCACT
CYP4A11	rs1126742(C > T)	F:GGCTGTGTTGAGCAGAACCC
		R:CCTGGCTCTGGTGCTCT

transplantations, the donor liver received has metabolic-function, and hence, liver transplantation is distinct from other solid organ transplantations, such as kidney and heart-transplantations. Theoretically, Tac metabolized in patients undergoing liver transplantation will be affected by CYP450 expression in both the recipient gastrointestinal tract and donor liver [6].

Therefore, we conducted a retrospective study to investigate the individual and combined effects of single-nucleotide polymorphisms (SNPs) in CYP2B6, CYP2C8, CYP2C9, CYP3A4, CYP3A5, and CYP4A11, which all belong to the CYP450 system. Both the short-term and long-term potential influences of variants in CYP450 genes of recipients and donors on individual pharmacological effects of Tac were evaluated in this study.

2. Materials and methods

2.1. Study design and population

Three hundred and seventy-three patients (male/female, 292/81) who underwent orthotopic liver transplantation between January 2015 and July 2017 were enrolled from two Chinese organ transplantation centers (the Affiliated Hospital of Qingdao University and Beijing You'an Hospital) in this retrospective cohort study (Supplement, Table 1). All patients were treated with a Tac-based immunosuppressive regimen. The average age of the patients was 51(44–58) years, and the average weight was 70(61–75) kg. Cases were eligible for inclusion in this study if they conformed to the inclusion criteria: 18–65 years old; Han ethnicity; no severe complications, such as acute rejection or severe infection. The exclusion criteria was as follows: retransplantation patients; combined organ transplantation patients; patients receiving co-medication drugs known to interfere with the transport and metabolism of FK506 or have a potential effect on drug metabolizing enzymes; medication nonadherence.

2.2. Data collection and C/D ratio evaluation

Liver transplantation recipient demographic information and laboratory data were collected retrospectively from electronic medical and patient medical records. Transplantation recipients weight (kg), daily dose (mg/d) and C_0 blood concentrations (ng/ml) of Tac on day 3, day 7, week 2, week 3, month 1, month 2, month 3, month 4, month 6 and 1 year after the initial administration were recorded. Then dose per weight (mg/kg/d) and blood concentrations of Tac for dose-administered [C/D ratio, (ng/ml)/(mg/kg/d)] patients could be calculated.

Donor and recipient genomic DNA was isolated from paraffin-embedded liver sections using an FFPE Tissue DNA Extraction Kit (BioTeke Corporation, Peking, China, cat.DP7211). Bio-Mark™ the Juno 96.96 Genotyping IFC (Fluidigm, US) was used for SNP genotyping. Polymerase chain reaction (PCR) primers are listed in Table 1. Three hundred and seventy-three liver transplantation patients and their