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Therapeutic Drug Monitoring of Blood Sirolimus and Tacrolimus Concentrations for Polypharmacy Management in a Lymphangioleiomyomatosis Patient Taking Two Cytochrome P450 3A Inhibitors

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Patients with lymphangioleiomyomatosis (LAM) and lung transplantations are treated with multiple drugs, such as tacrolimus, mycophenolate mofetil, prednisolone, and itraconazole, for long-term suppression of rejection response and prevention of infection. Additional drugs are required when lung transplant recipients develop graft complications. Therefore, managing polypharmacy is critical because of drug–drug interactions caused by various factors, including drug-metabolizing enzymes such as cytochrome P450 3A (CYP3A). The patient was a 48-year-old woman (height 144.9 cm and weight 38.4 kg) who underwent lung transplantation for LAM. Mycophenolate mofetil, tacrolimus (target blood concentration, 4.0-8.0 ng/mL), and prednisolone were administered for immunosuppression, and itraconazole and clarithromycin were administered to manage graft infection. The patient developed unilateral lymphedema, predominantly in the left leg; therefore, sirolimus was initiated with a target blood concentration of 3.0-5.0 ng/mL. In addition to 1.0 mg/day of sirolimus, tacrolimus (0.3 mg/day), itraconazole (100 mg/day), and clarithromycin (800 mg/day) were added. Blood sirolimus concentrations ranged from 18.8 to 36.9 ng/mL on days 6 to 9; thus, treatment with sirolimus was stopped because of over-target blood concentrations. Blood concentrations of sirolimus and tacrolimus were successfully managed without adverse events using therapeutic drug monitoring (TDM) and azole anti-fungal substitution of azithromycin instead of clarithromycin although sirolimus concentration was relatively lower compared to the target range. Thereby, frequent TDM, management of polypharmacy that influences CYP3A activity, and possibly *CYP3A* genotyping should be appropriately conducted for personalized medicine.

Keywords: cytochrome P450 3A; drug–drug interactions; lung transplantation; lymphangioleiomyomatosis; therapeutic drug monitoring
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Introduction

Lymphangioleiomyomatosis (LAM) is a rare progressive multisystem disorder that predominantly impacts women of reproductive age (Ferrans et al. 2000; Taveira-DaSilva and Moss 2015). Smooth muscle-resembling neoplastic spindle cells proliferate in various organs, such as the lungs, lymph nodes, and kidneys, resulting in shortness of breath or respiratory failure (Ferrans et al. 2000; Taveira-DaSilva and Moss 2015). Lung transplantation is considered, for instance, when the forced expiratory volume in one second reaches less than 30% of that predicted (Ando et al. 2016). After lung transplantation, triple immunosuppression (calcineurin inhibitors, anti-proliferative agents,

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and corticosteroids) regimens are employed as standard life-saving procedures (Scheffert and Raza 2014). In contrast, the LAM Foundation (2022) recommends long-term mTOR inhibition therapy using sirolimus or everolimus. In particular, the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus trial proves the priority of using sirolimus for LAM patients (McCormack et al. 2011). Therapeutic drug monitoring (TDM) has been used for both calcineurin and mTOR inhibitors, as well as mycophenolate mofetil, because of their narrow therapeutic window (MacDonald et al. 2000; Mohammadpour et al. 2011). Management of varying blood drug concentrations is critical because of numerous factors, including drug–drug interactions (DDIs) caused by drug-metabolizing enzymes.

Cytochrome P450 3A (CYP3A) is one of the primary metabolic enzymes involved in more than 30% of clinically useful drugs, including sirolimus and tacrolimus (Rosso Felipe et al. 2009; Zanger and Schwab 2013). The inter-individual variation influences the required sirolimus or tacrolimus dosage in CYP3A activities caused by *CYP3A* genetic variation and DDIs (Huang et al. 2008; Hendriks et al. 2020). United States Food and Drug Administration (FDA) (2022) summarizes substrates, inducers, and inhibitors for each CYP and transporter. Grapefruit juice, azole anti-fungals, macrolides, and verapamil are a few of the many CYP3A4 inhibitors listed by the FDA. Inadequate TDM of patients taking CYP3A4 inhibitors can lead to adverse drug reactions caused by elevated drug concentrations. Although the influence for blood tacrolimus and sirolimus concentrations by taking each azole anti-fungal in a single dose was reported (Kuypers et al. 2005; Said et al. 2006; Quinney et al. 2013; Matsuda et al. 2022), there is little evidence of an increase in the degree of CYP3A inhibition after dual administrations of azole antifungals given the rarity of the cases.

Here, we report a case of a patient taking two CYP3A inhibitors (itraconazole and clarithromycin) after starting sirolimus treatment. Tacrolimus dosage should also be managed during the combined administration of sirolimus and tacrolimus. Furthermore, *CYP3A* genetic polymorphisms were tested for a more detailed analysis of inter-individual differences in CYP3A activity.

Case Presentation

The patient was a 48-year-old woman (height 144.9 cm and weight 38.4 kg) who had undergone lung transplantation because of the development of LAM. Following the living-donor lung transplantation before 14 years, the recipient has been on mycophenolate mofetil, tacrolimus (target blood concentration, 4.0-8.0 ng/mL), prednisolone, and itraconazole for immunosuppression and prophylaxis for aspergillosis. Since the patient was diagnosed with non-tuberculous mycobacteria (NTM), clarithromycin with levofloxacin and ethambutol has been used for several years. Clinical laboratory values were as follows: vital capacity, 1.86 L (69.9% predicted); forced vital capacity, 1.94 L (76.4% predicted); forced expiratory volume in one second, 1.66 L (76.5% predicted); 6-min walk distance, 438 m; minimal arterial oxygen saturation of pulse oximetry, 85.0%; and modified Borg scores, 0.5 out of 10. This year, the patient developed unilateral lymphedema predominantly in the left leg; therefore, the underlying disease was treated with sirolimus (target blood concentration, 3.0-5.0 ng/mL) instead of mycophenolate mofetil. The clinical course of the patient is summarized in Fig. 1.

First, 1.0 mg/day of sirolimus was taken as a single dose along with tacrolimus (0.3 mg/day), itraconazole (100 mg/day), and clarithromycin (800 mg/day). On days 6-9, blood sirolimus concentrations ranged from 18.8 to 36.9 ng/mL, and sirolimus was stopped on day 6 because of elevated blood sirolimus concentrations. The concentration/dose ratios (C/D) were defined as sirolimus and tacrolimus concentrations per dose amount 3 days before sampling following a previous report (Kikuchi et al. 2019), because we considered the half-life of each drug and sirolimus was not administrated every day (Fig. 1). The C/D ratio of sirolimus was increased to approximately 20 ng/mL/dose amounts on day 9 (Fig. 2). Clarithromycin, a potent CYP3A inhibitor, was replaced with azithromycin on day 15. The patient resumed taking sirolimus (1.0 mg/mL) at the intervals shown in Fig. 1. However, blood tacrolimus concentrations should be considered because of antibiotic changes. Tacrolimus dosage was increased over several days to ensure CYP3A inhibition by itraconazole only, resulting in an adjustment of tacrolimus dosage to 2.8 mg daily (Fig. 1). Therefore, the C/D ratios of tacrolimus were changed to 0.5-0.8 from 5.8-8.9 ng/mL/dose amounts (Fig. 2). The dosage of both immunosuppressants was adjusted and lymphedema, predominantly in the left leg, disappeared on day 28. Blood sirolimus concentrations were stabilized at approximately 1.0 ng/mL (C/D ratios were 0.8-1.4 ng/mL/dose amounts) without any adverse events, although this value was lower than the target concentrations. Furthermore, there were no critical changes in the clinical laboratory values from day 0.

Blood samples were collected immediately before the morning doses. The blood concentrations of sirolimus were measured using an antibody-conjugated magnetic immunoassay with the Siemens Dimension Xpand Plus analyzer (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) according to the manufacturer's protocols. Blood tacrolimus concentrations were determined by chemiluminescence magnetic microparticle immunoassay using an Architect i2000SR analyzer (Abbott Diagnostics, North Chicago, IL, USA) according to the manufacturer's protocols. The clinical course of blood sirolimus and tacrolimus concentrations and C/D of sirolimus and tacrolimus are shown in Figs. 1 and 2. Additionally, we performed genetic polymorphism analysis according to a previously described method via Sanger sequencing using a polymerase chain reaction amplicon with minor modifications (Kumondai et al. 2021).

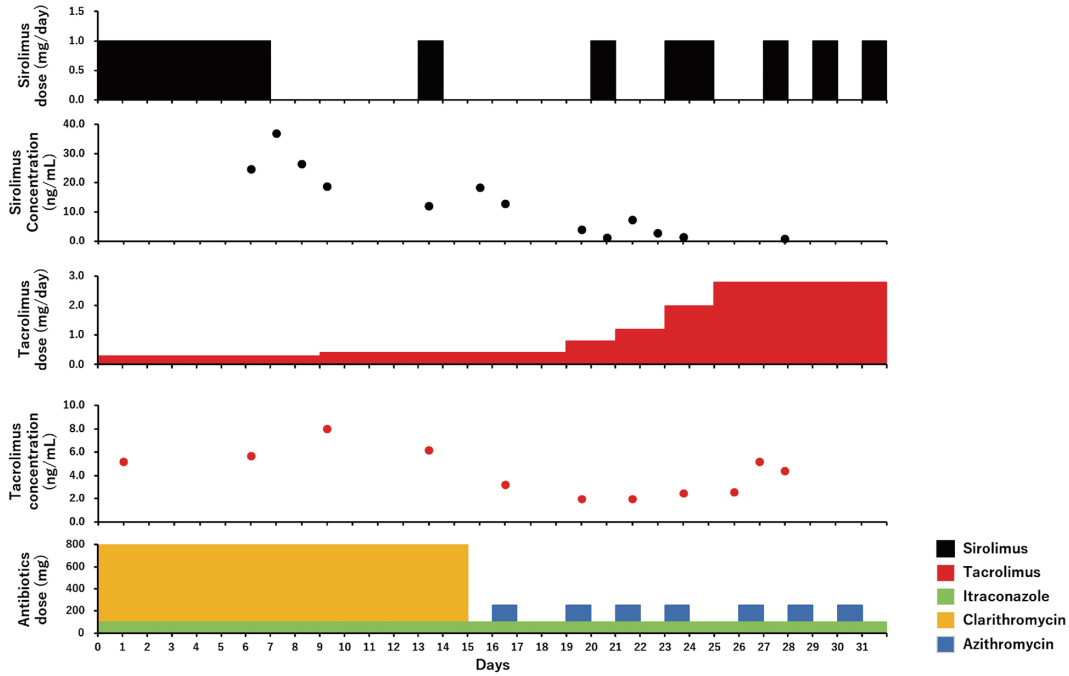

Fig. 1. Patient clinical course.
Daily sirolimus doses and blood concentrations are shown in black. Daily tacrolimus doses and blood concentrations are shown in red. Daily doses of each antibiotic are shown in green (itraconazole), yellow (clarithromycin), and blue (azithromycin).

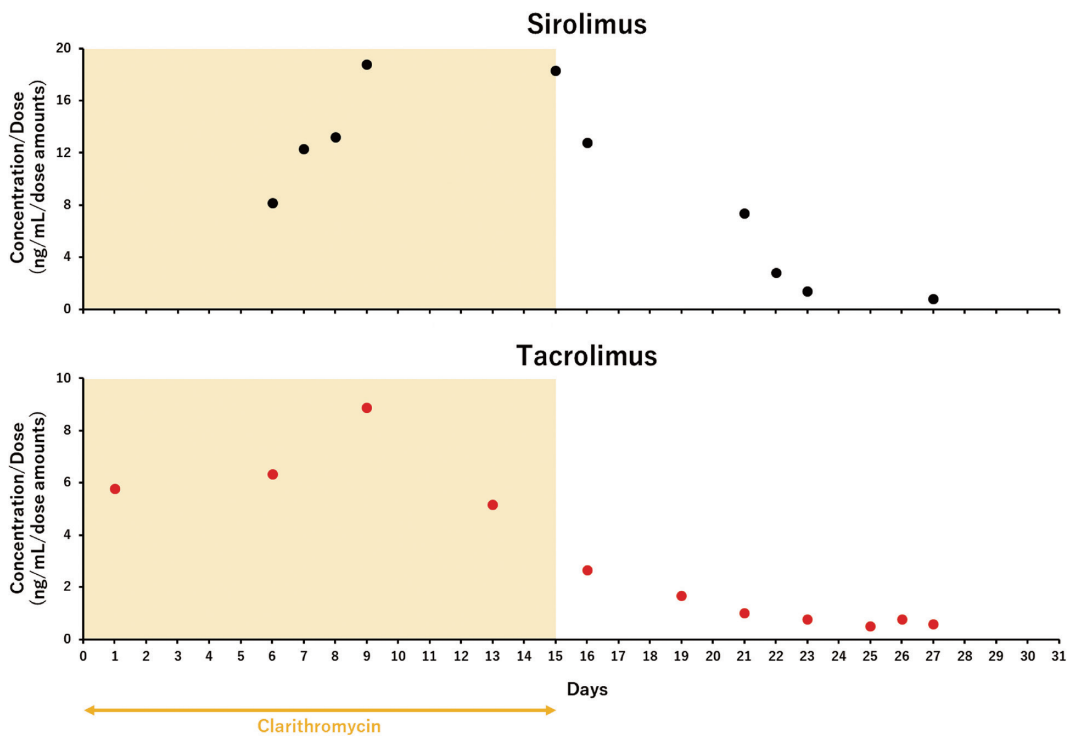

Fig. 2. Concentration/dose ratios of sirolimus and tacrolimus.
Dose amounts 3 days before sampling were used for the calculations. The period of taking clarithromycin is shown as a yellow background.

The patient was determined to have a *CYP3A5*1/*3* (rs776746, g.6986A>G) genotype, as shown in Fig. 3. However, no mutation in each *CYP3A4* exon region was observed; therefore, the patient was determined to have wild-type *CYP3A4*.

The participant provided written informed consent,

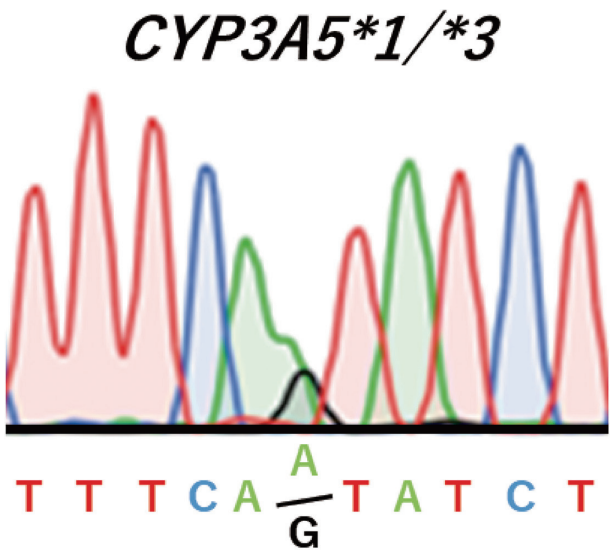

Fig. 3. Sanger sequencing confirming the patient's *CYP3A5* genotype.
The patient had a *CYP3A5*1/*3* genotype owing to them carrying a heterologous A>G mutation.

and the study was approved by the Ethics Review Board of Tohoku University Hospital (approval number 2021-1-928). The patient gave her consent for the publication of this report.

Discussion

Immunosuppressive therapy after lung transplantation is necessary for preventing rejection (Ferrans et al. 2000; Scheffert and Raza, 2014; Taveira-DaSilva and Moss 2015; Ando et al. 2016). Antibiotics, such as itraconazole, are also essential to control active infection. In this case, the patient developed NTM pulmonary disease post-transplantation. Therefore, clarithromycin was used longer, and blood tacrolimus concentrations were suitably controlled for the term. Because of its narrow therapeutic window, sirolimus concentrations should be monitored frequently and closely when it is initiated for treating LAM. Importantly, this is the rare case wherein two CYP3A inhibitors were used for treatment even if few evidences of combinational administration have been reported. Therefore, more strict dosage management of sirolimus and tacrolimus would be required for such patients.

In patients with LAM, DDIs caused by CYP3A inhibitors are a primary concern (Huang et al. 2008). The patient ingested two CYP3A inhibitors (itraconazole and clarithromycin). Therefore, their effects on blood sirolimus and tacrolimus concentrations should have been considered. Itraconazole and three of its metabolites are potential CYP3A inhibitors that act by coordinating bonds with the heme located in the CYP3A activity site (Isoherranen et al. 2004). Clinically, the concentration-to-dose ratio of tacrolimus increases 2.7-fold when itraconazole is administered to lung transplantation patients (Matsuda et al. 2022). Moreover, the sirolimus dosage was decreased 2.5-5.0-fold because of DDIs between sirolimus and itraconazole; sirolimus has been discontinued in several cases of treatment with azole anti-fungals (Kuypers et al. 2005; Said et al. 2006). Although itraconazole should be considered for sirolimus and tacrolimus dosage, in this case, where 1.0 mg/day of sirolimus was initiated, its dosage should have been adjusted more carefully with frequent TDM.

Clarithromycin forms an intermediate metabolic complex with CYP3A, inhibiting CYP3A-mediated drug clearance (Quinney et al. 2013). According to FDA (2022) guidelines, clarithromycin is classified as a strong irreversible CYP3A inhibitor, whereas azithromycin is not clinically recognized as a CYP3A inhibitor. To avoid the severe DDIs between clarithromycin and sirolimus, which could result in a high sirolimus blood trough concentration, we selected azithromycin for its weak CYP3A inhibition. Importantly, CYP3A inhibition by clarithromycin continued for a few days (Quinney et al. 2010; Barve et al. 2015). Therefore, the tacrolimus dosage for the patient increased 7-fold (from 0.4 to 2.8 mg/day) for 6 days. After 4 days, clarithromycin was stopped, and blood tacrolimus concentrations were successfully controlled. Due to the alteration in azole antibiotic dosage, blood sirolimus concentrations were also influenced by administering sirolimus at 3 mg/week (1 mg every other day). The C/D ratios for sirolimus and tacrolimus, shown in Fig. 2, demonstrated that CYP3A inhibition continued for several days, suggesting that CYP3A substrate drug dosage should not be increased immediately after discontinuation of clarithromycin. Moreover, by discontinuing clarithromycin, the C/D ratios of sirolimus and tacrolimus decreased 8- and 4-fold, respectively.

This case also focused on *CYP3A* genetic polymorphisms even though *CYP3A* genotyping was not clinically performed. The patient was determined to have *CYP3A4* wild-type and *CYP3A5*1/*3* genotypes. CYP3A inhibitors such as itraconazole are generally used for transplantation patients. Therefore, CYP3A5 expression levels should not be overlooked because various substrates are metabolized by both CYP3A4 and CYP3A5, although their contributions differ among substrates (Quinney et al. 2013; Shirasaka et al. 2013; Vanhove et al. 2018). In heart or kidney transplant recipients, the tacrolimus C/D ratio for *CYP3A5*3/*3* carriers was 2.00-3.18-fold higher than that of *CYP3A5*1/*1* and *CYP3A5*1/*3* carriers (Lesche et al. 2014; Rojas et al. 2015). Moreover, *CYP3A4* and *CYP3A5* genotypes in heart transplant recipients are substantially influenced by tacrolimus because of their higher protein homology (Gijsen et al. 2013). In contrast, sirolimus pharmacokinetics in healthy Chinese volunteers was affected by both genetic polymorphisms (Zhang et al. 2017). Although CYP3A activity is an important factor for sirolimus and tacrolimus dosage determination, the current patient was not a CYP3A-poor metabolizer; therefore, DDIs were crucial for adjusting sirolimus and tacrolimus dosages. However, more detailed evidence is required for CYP3A-

poor metabolizers because CYP3A activity is predicted to be more influential (Niioka et al. 2015). Dosage adjustment of sirolimus and tacrolimus for CYP3A5 non-expressor (*CYP3A5*3/*3*) patients should be considered more carefully due to CYP3A4 inhibition, although *CYP3A5*1* carriers can alternatively metabolize sirolimus and tacrolimus in case of CYP3A4 inhibition.

In summary, we report a case of the management of sirolimus and tacrolimus dosage in a patient taking two CYP3A inhibitors (itraconazole and clarithromycin). Clarithromycin, a strong irreversible CYP3A inhibitor, is one of the most important factors affecting sirolimus and tacrolimus concentrations. Notably, CYP3A inhibition by itraconazole generally used for transplantation patients should not be overlooked in terms of dosage adjustment, although dose alteration of itraconazole was not considered in the present case. The patient was not a *CYP3A5*3/*3* carrier; however, *CYP3A* genotyping may play an important role in drug concentration management owing to the *CYP3A5*3* allele frequency (Gijsen et al. 2013; Rodriguez-Antona et al. 2022). In conclusion, healthcare workers should appropriately perform frequent TDM, polypharmacy management, and possibly *CYP3A* genotyping for personalized medicine tailored to the patient's healthcare needs.

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Author Contributions

Conceptualization, M. Kumondai, and M. Kikuchi; participated in the treatment of the patient; A.M., M.U., T.H., and Y.O.; genotyping and visualization, M. Kumondai and N.H.; writing-original draft preparation, M. Kumondai; writing-review and editing, M. Kikuchi, A.M., N.H., T.H., Y.O., Y.S., T.S., M.M., and N.M.; and supervision, Y.S., T.S., M.M., and N.M. All authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

Ando, K., Okada, Y., Akiba, M., Kondo, T., Kawamura, T., Okumura, M., Chen, F., Date, H., Shiraishi, T., Iwasaki, A., Yamasaki, N., Nagayasu, T., Chida, M., Inoue, Y., Hirai, T., et al. (2016) Lung transplantation for lymphangioleiomyomatosis in Japan. *PLoS One*, **11**, e0146749.

Barve, A., Kovacs, S.J., Ke, J., Crabbe, R., Grosgurin, P., Menetrey, A., Nicolas-Metral, V., Dabovic, K., Dole, K., Zhang, J., Praestgaard, J., Sunkara, G. & Stein, D. (2015) The effects of CYP3A4 induction and inhibition on the pharmacokinetics of alisporivir in humans. *Clin. Pharmacol. Drug Dev.*, **4**, 25-32.

FDA (United States Food & Drug Administration) (2022) Drug development and drug interactions | Table of substrates, inhibitors and inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers [*Accessed*: December 12, 2022]

Ferrans, V.J., Yu, Z.X., Nelson, W.K., Valencia, J.C., Tatsuguchi, A., Avila, N.A., Riemenschn, W., Matsui, K., Travis, W.D. & Moss, J. (2000) Lymphangioleiomyomatosis (LAM): a review of clinical and morphological features. *J. Nippon Med. Sch.*, **67**, 311-329.

Gijsen, V.M., van Schaik, R.H., Elens, L., Soldin, O.P., Soldin, S.J., Koren, G. & de Wildt, S.N. (2013) CYP3A4*22 and CYP3A combined genotypes both correlate with tacrolimus disposition in pediatric heart transplant recipients. *Pharmacogenomics*, **14**, 1027-1036.

Hendriks, D.F.G., Vorrink, S.U., Smutny, T., Sim, S.C., Nordling, A., Ullah, S., Kumondai, M., Jones, B.C., Johansson, I., Andersson, T.B., Lauschke, V.M. & Ingelman-Sundberg, M. (2020) Clinically relevant cytochrome P450 3A4 induction mechanisms and drug screening in three-dimensional spheroid cultures of primary human hepatocytes. *Clin. Pharmacol. Ther.*, **108**, 844-855.

Huang, S.M., Strong, J.M., Zhang, L., Reynolds, K.S., Nallani, S., Temple, R., Abraham, S., Habet, S.A., Baweja, R.K., Burckart, G.J., Chung, S., Colangelo, P., Frucht, D., Green, M.D., Hepp, P., et al. (2008) New era in drug interaction evaluation: US Food and Drug Administration update on CYP enzymes, transporters, and the guidance process. *J. Clin. Pharmacol.*, **48**, 662-670.

Isoherranen, N., Kunze, K.L., Allen, K.E., Nelson, W.L. & Thummel, K.E. (2004) Role of itraconazole metabolites in CYP3A4 inhibition. *Drug Metab. Dispos.*, **32**, 1121-1131.

Kikuchi, M., Shigeta, K., Tanaka, M., Takasaki, S., Akiba, M., Oishi, H., Sado, T., Matsuda, Y., Noda, M., Okada, Y., Mano, N. & Yamaguchi, H. (2019) Estimation of blood sirolimus concentration based on tacrolimus concentration/dose normalized by body weight ratio in lung transplant patients. *Ther. Drug Monit.*, **41**, 615-619.

Kumondai, M., Gutierrez Rico, E.M., Hishinuma, E., Ueda, A., Saito, S., Saigusa, D., Tadaka, S., Kinoshita, K., Nakayoshi, T., Oda, A., Abe, A., Maekawa, M., Mano, N., Hirasawa, N. & Hiratsuka, M. (2021) Functional characterization of 40 CYP3A4 variants by assessing midazolam 1'-hydroxylation and testosterone 6beta-hydroxylation. *Drug Metab. Dispos.*, **49**, 212-220.

Kuypers, D.R., Claes, K., Evenepoel, P., Maes, B., Vandecasteele, S., Vanrenterghem, Y., Van Damme, B. & Desmet, K. (2005) Drug interaction between itraconazole and sirolimus in a primary renal allograft recipient. *Transplantation*, **79**, 737.

Lesche, D., Sigurdardottir, V., Setoud, R., Oberhansli, M., Carrel, T., Fiedler, G.M., Largiader, C.R., Mohacsi, P. & Sistonen, J. (2014) CYP3A5*3 and POR*28 genetic variants influence the required dose of tacrolimus in heart transplant recipients. *Ther. Drug Monit.*, **36**, 710-715.

MacDonald, A., Scarola, J., Burke, J.T. & Zimmerman, J.J. (2000) Clinical pharmacokinetics and therapeutic drug monitoring of sirolimus. *Clin. Ther.*, **22** Suppl B, B101-121.

Matsuda, Y., Nakagawa, S., Yano, I., Masuda, S., Imai, S., Yonezawa, A., Yamamoto, T., Sugimoto, M., Tsuda, M., Tsuzuki, T., Omura, T., Nakagawa, T., Chen-Yoshikawa, T.F., Nagao, M., Date, H., et al. (2022) Effect of itraconazole and its metabolite hydroxyitraconazole on the blood concentrations of cyclosporine and tacrolimus in lung transplant recipients. *Biol. Pharm. Bull.*, **45**, 397-402.

McCormack, F.X., Inoue, Y., Moss, J., Singer, L.G., Strange, C.,

Nakata, K., Barker, A.F., Chapman, J.T., Brantly, M.L., Stocks, J.M., Brown, K.K., Lynch, J.P. 3rd, Goldberg, H.J., Young, L.R., Kinder, B.W., et al. (2011) Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N. Engl. J. Med.*, **364**, 1595-1606.

Mohammadpour, N., Elyasi, S., Vahdati, N., Mohammadpour, A.H. & Shamsara, J. (2011) A review on therapeutic drug monitoring of immunosuppressant drugs. *Iran J. Basic Med. Sci.*, **14**, 485-498.

Niioka, T., Kagaya, H., Saito, M., Inoue, T., Numakura, K., Habuchi, T., Satoh, S. & Miura, M. (2015) Capability of utilizing CYP3A5 polymorphisms to predict therapeutic dosage of tacrolimus at early stage post-renal transplantation. *Int. J. Mol. Sci.*, **16**, 1840-1854.

Quinney, S.K., Malireddy, S.R., Vuppalanchi, R., Hamman, M.A., Chalasani, N., Gorski, J.C. & Hall, S.D. (2013) Rate of onset of inhibition of gut-wall and hepatic CYP3A by clarithromycin. *Eur. J. Clin. Pharmacol.*, **69**, 439-448.

Quinney, S.K., Zhang, X., Lucksiri, A., Gorski, J.C., Li, L. & Hall, S.D. (2010) Physiologically based pharmacokinetic model of mechanism-based inhibition of CYP3A by clarithromycin. *Drug Metab. Dispos.*, **38**, 241-248.

Rodriguez-Antona, C., Savieo, J.L., Lauschke, V.M., Sangkuhl, K., Drogemoller, B.I., Wang, D., van Schaik, R.H.N., Gilep, A.A., Peter, A.P., Boone, E.C., Ramey, B.E., Klein, T.E., Whirl-Carrillo, M., Pratt, V.M. & Gaedigk, A. (2022) PharmVar GeneFocus: CYP3A5. *Clin. Pharmacol. Ther.*, **112**, 1159-1171.

Rojas, L., Neumann, I., Herrero, M.J., Boso, V., Reig, J., Poveda, J.L., Megias, J., Bea, S. & Alino, S.F. (2015) Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. *Pharmacogenomics J.*, **15**, 38-48.

Rosso Felipe, C., de Sandes, T.V., Sampaio, E.L., Park, S.I., Silva, H.T. Jr. & Medina Pestana, J.O. (2009) Clinical impact of polymorphisms of transport proteins and enzymes involved in the metabolism of immunosuppressive drugs. *Transplant. Proc.*, **41**, 1441-1455.

Said, A., Garnick, J.J., Dieterle, N., Peres, E., Abidi, M.H. & Ibrahim, R.B. (2006) Sirolimus-itraconazole interaction in a hematopoietic stem cell transplant recipient. *Pharmacotherapy*, **26**, 289-295.

Scheffert, J.L. & Raza, K. (2014) Immunosuppression in lung transplantation. *J. Thorac. Dis.*, **6**, 1039-1053.

Shirasaka, Y., Chang, S.Y., Grubb, M.F., Peng, C.C., Thummel, K.E., Isoherranen, N. & Rodrigues, A.D. (2013) Effect of CYP3A5 expression on the inhibition of CYP3A-catalyzed drug metabolism: impact on modeling CYP3A-mediated drug-drug interactions. *Drug Metab. Dispos.*, **41**, 1566-1574.

Taveira-DaSilva, A.M. & Moss, J. (2015) Clinical features, epidemiology, and therapy of lymphangioleiomyomatosis. *Clin. Epidemiol.*, **7**, 249-257.

The LAM Foundation (2022) LAM Management. https://www.thelamfoundation.org/Healthcare-Providers/Diagnosis-Treatment/LAM-Management [*Accessed*: December 6, 2022]

Vanhove, T., de Jonge, H., de Loor, H., Oorts, M., de Hoon, J., Pohanka, A., Annaert, P. & Kuypers, D.R.J. (2018) Relationship between in vivo CYP3A4 activity, CYP3A5 genotype, and systemic tacrolimus metabolite/parent drug ratio in renal transplant recipients and healthy volunteers. *Drug Metab. Dispos.*, **46**, 1507-1513.

Zanger, U.M. & Schwab, M. (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol. Ther.*, **138**, 103-141.

Zhang, J., Dai, Y., Liu, Z., Zhang, M., Li, C., Chen, D. & Song, H. (2017) Effect of CYP3A4 and CYP3A5 genetic polymorphisms on the pharmacokinetics of sirolimus in healthy Chinese volunteers. *Ther. Drug Monit.*, **39**, 406-411.