Association of P450 Oxidoreductase Gene Polymorphism with Tacrolimus Pharmacokinetics in Renal Transplant Recipients: A Systematic Review and Meta-Analysis

Da-Hoon Lee 1, Hana Lee 2, Ha-Young Yoon 1, Jeong Yee 1,* and Hye-Sun Gwak 1,*\

1 College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, Korea; hhooolnn@ewhaeain.net (D.-H.L.); hayoungdymphmayoon@gmail.com (H.-Y.Y.)
2 Graduate School of Clinical Biohealth, Ewha Womans University, Seoul 03760, Korea; lhn09345@naver.com
* Correspondence: jjhelly1@naver.com (J.Y.); hsgwak@ewha.ac.kr (H.-S.G.); Tel.: +82-2-3277-3052 (J.Y.);
+82-2-3277-4376 (H.-S.G.)

Abstract: There are conflicting results regarding the effect of the P450 oxidoreductase (POR) *28 genotype on the tacrolimus (TAC) pharmacokinetics (PKs) during the early post-transplantation period in adult renal transplant recipients. Thus, we characterized the impact of POR*28 on TAC PKs. We conducted a systematic review on the association between POR*28 and PKs of TAC in adult renal transplant recipients. Structured searches were conducted using PubMed, Web of Science, and Embase. TAC standardized trough concentration (ng/mL per mg/kg) data were extracted. Mean differences (MD) and their corresponding 95% confidence intervals (CIs) were used to identify the differences between the POR*28 genotype and PKs of TAC. The subgroup analysis was conducted according to CYP3A5 expression status. Six studies (n = 1061) were included. TAC standardized trough concentrations were significantly lower in recipients with the POR*28 allele compared to recipients with POR*1/*1 (MD: 8.30 ng/mL per mg/kg; 95% CI: 1.93, 14.67; p = 0.01). In the subgroup analysis, TAC standardized trough concentrations were lower for subjects who were POR*28 carriers than those who were POR*1/*1 in CYP3A5 expressers (MD: 20.21 ng/mL per mg/kg; 95% CI: 16.85, 23.56; p < 0.00001). No significant difference between POR*28 carriers and POR*1/*1 was found in the CYP3A5 non-expressers. The results of our meta-analysis demonstrated a definite correlation between the POR*28 genotype and PKs of TAC. Patients carrying the POR*28 allele may require a higher dose of TAC to achieve target levels compared to those with POR*1/*1, especially in CYP3A5 expressers.

Keywords: tacrolimus; POR; pharmacokinetics; kidney transplant

1. Introduction

Tacrolimus (TAC), one of the calcineurin inhibitors, is commonly used as an immuno-suppressant to prevent acute organ rejection after kidney transplantation [1]. TAC has a narrow therapeutic index and wide interindividual pharmacokinetic (PK) variability. Thus, TAC administration requires therapeutic drug monitoring (TDM) to enhance efficacy and to avoid side effects [1–4]. Although TDM is widely practiced, some patients are exposed to sub- or supra-therapeutic concentrations of TAC, thereby increasing their risk of acute organ rejection or toxicity within a week after transplantation [5].

TAC is metabolized by cytochrome P450 (CYP), especially CYP3A5 [6]. CYP3A5*3 (c.219-237A>G; rs776746) is a critical predictor of CYP3A5 activity [7,8], and several studies reported that CYP3A5 non-expressers (CYP3A5*3/*3) are related to decreased metabolizing functions and higher TAC trough concentrations compared with CYP3A5 expressers (CYP3A5*1/*1 or CYP3A5*1/*3) [9–12].

Recently, further attention has been given to P450 oxidoreductase (POR), which transfers electrons from nicotinamide-adenine-dinucleotide phosphate-oxidase to CYP enzymes,
inducing CYP expression and affecting TAC metabolism [13,14]. Among several single nucleotide polymorphisms (SNPs) of POR, the most common variant is POR*28 (c.1508 C>T, rs1057868). According to an in vitro study, this SNP was associated with increased CYP activity, including CYP1A2, CYP2C19, CYP3A4, and CYP3A5 [15]. Previous studies have investigated the role of POR*28 in the Pks of TAC and reported that patients carrying POR*28 exhibited lower trough concentrations of TAC and required higher TAC doses than wild-type patients (POR*1/*1) [16–18]. However, the results of previous studies are conflicting due to their small sample sizes. Therefore, we conducted a systematic review and meta-analysis of the existing studies to determine the effects of POR*28 on TAC trough concentrations in renal transplant patients.

2. Materials and Methods

2.1. Search Strategy and Study Selection

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. We performed a comprehensive search of three electronic databases (PubMed, Web of Science, and Embase) on 16 July 2021 using the following search terms: (tacrolimus OR FK506 OR FK-506 OR (calcineurin inhibitor) OR Prograf OR immunosuppress*) AND ((kidney transplant*) OR (kidney graft*) OR (kidney allograft*) OR (renal transplant*) OR (renal graft*) OR (renal allograft*)) AND (POR OR (p450 oxidoreductase) OR (cytochrome p450 oxidoreductase) OR CYPOR) AND (polymorph* OR variant* OR mutation* OR genotyp* OR phenotyp* OR haplotyp* OR SNP OR rs1057868 OR Ala503Val OR A503V) (Table 1).

| No | Search Term                                                                 | PubMed  | Web of Science | Embase  |
|----|----------------------------------------------------------------------------|---------|----------------|---------|
| #1 | (tacrolimus) OR (FK506) OR (FK-506) OR (calcineurin inhibitor) OR (Prograf) OR (immunosuppress*) | 481,508 | 153,419        | 391,339 |
| #2 | (kidney transplant*) OR (kidney graft*) OR (kidney allograft*) OR (renal transplant*) OR (renal graft*) OR (renal allograft*) | 190,248 | 202,994        | 324,655 |
| #3 | (POR) OR (P450 oxidoreductase) OR (cytochrome P450 oxidoreductase) OR (CYPOR) | 138,663 | 16,910         | 70,583  |
| #4 | (polymorph*) OR (variant*) OR (mutation*) OR (genotyp*) OR (phenotyp*) OR (haplotyp*) OR (SNP) OR (rs1057868) OR (Ala503Val) OR (A503V) | 2,146,909 | 2,144,583 | 2,821,213 |
| #5 | #1 and #2                                                                 | 48,448  | 31,892         | 78,405  |
| #6 | #4 and #5                                                                 | 25,468  | 1794           | 3279    |
| #7 | #3 and #6                                                                 | 460     | 53             | 73      |

Studies were selected if (1) the studies focused on the effects of the POR*28 genotype on renal transplant patients receiving TAC; (2) the studies had TAC PK data expressed as standardized trough concentration (ng/mL per mg/kg); and (3) the articles were published in English. Standardized trough concentration was determined as the concentration adjusted by the dose per body weight. Studies were excluded if they were (1) abstracts, reviews, editorials, or letters; (2) in vitro or in vivo studies; (3) studies performed on pediatric patients; or (4) studies from which we were unable to extract outcome data.

After removing duplicate studies, two authors independently excluded irrelevant studies by reviewing the titles and abstracts. Then, full-text articles were assessed for inclusion. Any inconsistencies were resolved by consensus between the two authors.

2.2. Data Extraction and Study Quality Assessment

Two reviewers independently extracted data using a preconceived data extraction spreadsheet. The following information was included: name of the first author, publication
year, ethnicity, patient numbers, percentage of males, mean age, mean body weight, follow-up day, TAC initial dose, target trough level, concomitant drugs, and method of genotyping and quantification. Two reviewers assessed the study’s quality using the Newcastle–Ottawa scale (NOS) tool [20]. The NOS tool is based on three domains: the selection of exposed and unexposed subjects (0–4 points), comparability of study groups (0–2 points), and outcome assessment (0–3 points). In terms of comparability, if CYP3A5 expression and age were adjusted for the analysis, we rated them with 1 point for each.

2.3. Statistical Analysis

Mean differences (MD) and their corresponding 95% confidence intervals (CIs) were used to identify the differences between the POR*28 genotype and PKs of TAC, and the Z-test was performed to detect the statistically significant differences between two groups. To calculate pooled estimates, we extracted the mean and standard deviation. If the studies only reported the median and interquartile range, the formulas by Wan et al. [21] were used to estimate the mean and standard deviation. Data presented as log-transformed mean and standard deviation were converted to the raw scale using the methodology of Higgins et al. [22].

We assessed the heterogeneity across studies using the chi-square test and I² statistics [23], and I² > 50% was regarded as indicating significant heterogeneity. The fixed-effect model was used if there was no significant heterogeneity; otherwise, the random-effects model was used. When we confirmed heterogeneity, a sensitivity analysis was conducted by omitting each study in turn to assess the influence of individual studies. To detect publication bias, Begg’s rank correlation test and Egger’s regression test were performed using R Studio software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) [24,25]. As the effects of POR*28 can depend on the expression status of CYP3A5, a subgroup analysis was conducted according to CYP3A5 expression status. The meta-analysis was performed using Review Manager 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was defined as a p-value < 0.05.

3. Results

Our initial search yielded 586 studies, 501 of which remained after duplicates were removed. After excluding 451 articles based on their titles and abstracts, we assessed the full text of 50 studies. Among them, 44 studies were excluded for the following reasons: evaluating other genotypes (n = 20), not having concentration data with adjustment by body weight (n = 11), not an original article (n = 6), evaluating other outcomes (n = 5), and not able to extract data (n = 2). Finally, six studies [26–31] involving 1061 patients were included in the meta-analysis (Figure 1). The characteristics of these studies are summarized in Table 2. The studies were published between 2014 and 2018, and all were cohort studies. Four of the six studies were conducted with Asian populations, one with Caucasians, and the other with multiethnic groups. The mean age of the patients was 43.3 years (range 40.0–49.5). Quality scores evaluated using the NOS ranged from 7 to 9.

The results of a meta-analysis investigating POR*28 and standardized trough concentrations of TAC are shown in Figure 2. POR*28 carriers showed a 8.30 ng/mL per mg/kg lower concentration of TAC when compared with POR*1/*1 carriers (95% CI: 1.93, 14.67; p = 0.01; I² = 55%). The funnel plot was asymmetrical (Figure 3), and Begg’s test and Egger’s test indicated no evidence of publication bias (p = 0.573 and p = 0.293, respectively). In the sensitivity analysis, the exclusion of Liu et al. led to a loss of statistical significance (Table 3).
The results of a meta-analysis investigating POR*28 and CYP3A5 expression status [26,27,29–31]. There were 270 CYP3A5 expressers (CYP3A5*1/*1 or *1/*3) and 550 CYP3A5 non-expressers (CYP3A5*3/*3). In the CYP3A5 expressing subgroup, the TAC standardized trough concentration was 20.21 ng/mL per mg/kg lower for POR*28 carriers (95% CI: 16.85, 23.56; p < 0.00001; I² = 50%; Figure 4a). However, in the CYP3A5 non-expressing subgroup, POR*28 was not associated with the TAC standardized trough concentration (MD: 4.12 ng/mL per mg/kg, 95% CI: –9.11, 0.86; p = 0.1; I² = 0%; Figure 4b).

Five studies reported the influence of the POR*28 genotype on the standardized trough concentrations of TAC according to CYP3A5 expression status [26,27,29–31]. There were 270 CYP3A5 expressers (CYP3A5*1/*1 or *1/*3) and 550 CYP3A5 non-expressers (CYP3A5*3/*3). In the CYP3A5 expressing subgroup, the TAC standardized trough concentration was 20.21 ng/mL per mg/kg lower for POR*28 carriers than for POR*1/*1 carriers (95% CI: 16.85, 23.56; p < 0.00001; I² = 50%; Figure 4a). However, in the CYP3A5 non-expressing subgroup, POR*28 was not associated with the TAC standardized trough concentration (MD: 4.12 ng/mL per mg/kg, 95% CI: –9.11, 0.86; p = 0.1; I² = 0%; Figure 4b).
Table 2. The characteristics of included studies.

| First Author, Year | Ethnic Background | N (Male) | Age, Year (SD) | Weight, kg (SD) | POR*28 Allele Frequency (%) | Post-Transplantation Day | Initial Dose | Target Trough Level, ng/mL | Coadministration Genotyping Methods | Genotyping Methods | Quantification Methods | NOS |
|--------------------|------------------|----------|----------------|-----------------|-----------------------------|--------------------------|--------------|-----------------------------|-----------------------------------|------------------|---------------------|-----|
| Elens et al., 2014 [26] | Caucasian, Asian, African-American, Others | 127 *(60.2) | 49.5 (15.3) | 72.6 (16.6) | 22.1 | 10 | NA | 5–15 | MMF or azathioprine, corticosteroids | TaqMan assay | MEIA | 9 |
| Kurzawski et al., 2014 [27] | Caucasian | 241 (55.6) | 45.8 (12.4) | 73.2 (13.9) | 26.4 | 7 | 100 ng/kg/day | 10–15 | MMF, corticosteroids | TaqMan assay | CMIA | 9 |
| Li et al., 2014 [28] | Asian | 240 (67.1) | 41.0 (12.2) | 57.9 (10.1) | 35.6 | 6–8 | 100 ng/kg, bid | 9–14 | MMF, steroids | SNaPshot assay | MEIA | 7 |
| Zhang et al., 2015 [29] | Asian | 83 (72.3) | 40.4 (11.3) | 62.0 (9.4) | 39.8 | 7 | NA | 10–15 | MMF, steroids | PCR-RFLP Emit 2000 Tacrolimus assay | 9 |
| Liu et al., 2016 [30] | Asian | 154 (NA) | 40.0 (10.9) | 59.8 (10.7) | 34.1 | 7 | 50–75 ng/kg, bid | 5–8 | MMF, prednisolone | PCR-RFLP MEIA | 8 |
| Phupradit et al., 2018 [31] | Asian | 216 (61.1) | 43.0 (14.6) | 57.1 (11.3) | 32.4 | 7 | 100 ng/kg/day | 4–8 | Mycophenolic acid, corticosteroids or basiliximab | TaqMan assay | CMIA | 9 |

*bid: twice a day; CMIA: chemiluminescent microparticle immunoassay; MEIA: microparticle enzyme immunoassay; MMF: mycophenolate mofetil; NA: not available; NOS: Newcastle–Ottawa score; PCR–RFLP: polymerase chain reaction–restriction fragment length polymorphism; SD: standard deviation. * Of the total population of 184, only 127 blood samples were obtained on day 10.
The results of a meta-analysis investigating POR*28 and CYP3A5 non-expressers (CYP3A5*3/*3). In the CYP3A5 expressing subgroup, the TAC standardized trough concentration was 20.21 ng/mL per mg/kg lower for POR*28 carriers than for CYP3A5 non-expressers.

Table 3. A sensitivity analysis of the association between POR*28 carriers and standardized trough concentration (ng/mL per mg/kg) of tacrolimus by sequentially excluding each study.

| Excluded Study | Heterogeneity I² (%) | Statistical Model | Mean Difference [95% CI] |
|----------------|---------------------|------------------|------------------------|
| None           | 55                  | Random           | −11.67 [−14.16, −9.19] |
| Elens et al., 2014 [26] | 62                  | Random           | −8.68 [−15.95, −1.42]  |
| Kurzawski et al., 2014 [27] | 53                  | Random           | −9.51 [−16.31, −2.70]  |
| Li et al., 2014 [28] | 52                  | Random           | −9.61 [−16.04, −3.17]  |
| Zhang et al., 2015 [29] | 54                  | Random           | −6.97 [−13.17, −0.76]  |
| Liu et al., 2016 [30] | 29                  | Fixed            | −5.38 [−11.17, 0.40]   |
| Phupradit et al., 2018 [31] | 58                  | Random           | −8.84 [−16.59, −1.09]  |

CI: confidence interval.

Figure 3. A funnel plot showing the association between POR*28 carriers and standardized trough concentration (ng/mL per mg/kg) of tacrolimus. SE: standard error, MD: mean difference.

Table 3. A sensitivity analysis of the association between POR*28 carriers and standardized trough concentration (ng/mL per mg/kg) of tacrolimus by sequentially excluding each study.

4. Discussion

This is the first meta-analysis investigating the association between the POR*28 polymorphism and the standardized initial trough concentration of TAC in adult renal transplant recipients. The results showed that POR*28 carriers had a lower standardized trough
concentration of TAC when compared with POR*1/*1 carriers. This association was increased in CYP3A5 expressers; however, POR*28 did not affect the TAC concentration in CYP3A5 non-expressers.

POR*28, a missense variant of POR, is the most common variant observed in about 28% of all alleles [32]. This variant is present in the flavin adenine dinucleotide (FAD) binding site, thereby affecting POR and CYP interactions [33]. In vitro studies demonstrated that POR*28 affects CYP3A4 activity in a substrate-specific manner [34,35]. Several PK studies demonstrated that POR*28 is related to increased CYP3A activity. The study of Oneda et al. [36], which investigated CYP3A in vivo activity using midazolam, showed that POR*28/28 was related to a 1.6-fold increase in hepatic CYP3A activity. Yang et al. [37] also showed that POR*28 was associated with increased hepatic CYP3A activity. In line with previous findings, our results regarding increased CYP3A activity might be explained by the effects of POR*28.

Several studies have reported that decreased exposure to TAC within a week after transplantation was associated with acute organ rejection. Kuypers et al. [38] reported that patients with an area under the concentration curve of 0–12 h (AUC(0–12)) below 200 ng·h/mL had a higher risk of acute rejection when compared with those with a higher AUC(0–12). Borobia et al. [39] also showed that patients with acute organ rejection had lower TAC trough concentrations than those without acute organ rejection. Our meta-analysis demonstrating that patients carrying the POR*28 allele had decreased TAC concentrations indicates POR*28 is an important factor in predicting acute organ rejection.

According to the subgroup analysis in this meta-analysis, POR*28 effects on the TAC concentration varied by CYP3A5 expression status, which is consistent with previous studies. For example, according to Jonge et al. [18], CYP3A5 expressers carrying the POR*28 allele required an approximately 25% higher TAC dose than CYP3A5 expressers with POR*1/*1, although the POR*28 allele did not affect TAC doses in CYP3A5 non-expressers. Gijsen et al. [40] reported that, in CYP3A5 expressers, patients with the POR*28 allele had an approximately 20% lower TAC concentration-to-dose ratio than those with POR*1/*1. However, the POR*28 polymorphism had no effect on the TAC concentration/dose ratio in CYP3A5 non-expressers. This can be explained by the role of POR, which provides electrons and enhances CYP activity.

Ethnicity may affect the expression of POR and thereby TAC metabolism. As the minor allele frequency of POR*28 was 20.0% in African Americans, 28.6% in Caucasians, and 38.9% in Asians [41], Asians are thought to be more affected by POR*28. Unfortunately, we could not compare the POR*28 effects by ethnicity, due to the small number of studies in non-Asian populations. Further studies are needed.

Our findings should be interpreted considering the following limitations. First, only six retrospective studies were included. Second, some heterogeneity existed, possibly due to the difference in the analytic methods used to determine concentrations and target concentrations. Last, although we used standardized trough concentrations after considering weight and dose, we could not adjust several factors (e.g., concurrent drugs), which can affect TAC concentrations, due to the lack of individual data.

Nevertheless, our meta-analysis demonstrated that the POR*28 polymorphism affects the TAC standardized trough concentration during the early post-transplantation period in adult renal transplant recipients, especially CYP3A5 expressers. POR and CYP3A5 genotyping might help to adjust appropriate TAC doses to reach target trough concentrations, leading to better treatment outcomes.

**Author Contributions:** Conceptualization, D.-H.L., J.Y. and H.-S.G.; methodology, D.-H.L., H.-Y.Y., J.Y. and H.-S.G.; formal analysis, D.-H.L., H.L. and H.-Y.Y.; investigation, D.-H.L., H.L., H.-Y.Y., J.Y. and H.-S.G.; writing—original draft preparation, D.-H.L., J.Y. and H.-S.G.; writing—review and editing, J.Y. and H.-S.G.; supervision, J.Y. and H.-S.G. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.
Institutional Review Board Statement: Ethical review and approval were waived for this study due to the nature of the systematic review article.

Informed Consent Statement: Patient consent was waived due to the nature of the systematic review article.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lesley, S. Tacrolimus, A further update of its use in the management of organ transplantation. *Drugs* 2003, 63, 1247–1297.
2. Felipe, C.R.; Silva, H.T.; Machado, P.G.; Garcia, R.; da Silva Moreira, S.R.; Pestana, J.O. The impact of ethnic miscegenation on tacrolimus clinical pharmacokinetics and therapeutic drug monitoring. *Clin. Transplant.* 2002, 16, 262–272. [CrossRef]
3. Taylor, A.L.; Watson, C.J.; Bradley, J.A. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Crit. Rev. Oncol./Hematol.* 2005, 56, 23–46. [CrossRef]
4. Venkataramanan, R.; Swaminathan, A.; Prasad, T.; Jain, A.; Zuckerman, S.; Warty, V.; McMichael, J.; Lever, J.; Burckart, G.; Starzl, T. Clinical pharmacokinetics of tacrolimus. *Clin. Pharmacokinet.* 1995, 29, 404–430. [CrossRef] [PubMed]
5. Laskow, D.A.; Vincenti, F.; Neylan, J.F.; Mendez, R.; Matas, A.J. An open-label, concentration-ranging trial of FK506 in primary kidney transplantation: A Report of the United States Multicenter FK506 Kidney Transplant Group1. *Transplantation* 1996, 62, 900–905. [CrossRef] [PubMed]
6. Anglicheau, D.; Verstuyft, C.; Laurent-Puig, P.; Becquemont, L.; Schlager, M.-H.; Cassinat, B.; Beaune, P.; Legendre, C.; Thervet, E. Association of the Multidrug Resistance-1 Gene Single-Nucleotide Polymorphisms with the Tacrolimus Dose Requirements in Renal Transplant Recipients. *J. Am. Soc. Nephrol.* 2003, 14, 1889–1896. [CrossRef]
7. Huster, E.; Haberl, M.; Burk, O.; Wolbold, R.; He, Y.-Q.; Klein, K.; Nuessler, A.C.; Neuhaus, P.; Klattig, J.; Eiselt, R.; et al. The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenetics* 2001, 11, 773–779. [CrossRef]
8. Kuehl, P.; Zhang, J.; Lin, Y.; Lamba, J.; Assem, M.; Schuetz, E. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat. Genet.* 2001, 27, 383–391. [CrossRef]
9. Mourad, M.; Mourad, G.; Wallmaq, P.; Garrigue, V.; Van Bellingen, C.; Van Kerckhove, V.; De Meyer, M.; Malaise, J.; Eddour, D.C.; Lison, D.; et al. Sirolimus and Tacrolimus Trough Concentrations and Dose Requirements after Kidney Transplantation in Relation to CYP3A5 and MDR1 Polymorphisms and Steroids. *Transplantation* 2005, 80, 977–984. [CrossRef] [PubMed]
10. Thervet, E.; Anglicheau, D.; King, B.; Schlager, M.H.; Cassinat, B.; Beaune, P.; Christophe, L.; Daly, A.K. Impact of cytochrome P450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients12. *Transplantation* 2003, 76, 1233–1235. [CrossRef] [PubMed]
11. Zheng, H.; Webber, S.; Zeevi, A.; Schuetz, E.; Zhang, J.; Bowman, P.; Boyle, G.; Law, Y.; Miller, S.; Lamba, J.; et al. Tacrolimus dosing in pediatric heart transplant patients is related to CYP3A5 and MDR1 gene polymorphisms. *Am. J. Transplant.* 2003, 3, 477–483. [CrossRef]
12. Goto, M.; Masuda, S.; Kiuchi, T.; Oyuga, Y.; Oike, F.; Okuda, M.; Tanaka, K.; Inui, K.-I. CYP3A5*1-carrying graft liver reduces the concentration/oral dose ratio of tacrolimus in recipients of living-donor liver transplantation. *Pharmacogenetics* 2004, 14, 471–478. [CrossRef]
13. Hubbard, P.A.; Shen, A.L.; Paschke, R.; Kasper, C.B.; Kim, J.J.P. NADPH-cytochrome P450 oxidoreductase: Structural basis for hydride and electron transfer. *J. Biol. Chem.* 2001, 276, 29163–29170. [CrossRef]
14. Masters, B.S.S. The journey from NADPH-cytochrome P450 oxidoreductase to nitric oxide synthases. *Biochem. Biophys. Res. Commun.* 2005, 338, 507–519. [CrossRef]
15. Agrawal, V.; Huang, N.; Miller, W.L. Pharmacogenetics of P450 oxidoreductase: Effect of sequence variants on activities of CYP1A2 and CYP2C19. *Pharm. Genom.* 2008, 18, 569–576. [CrossRef] [PubMed]
16. Lunde, I.; Bremer, S.; Midtvedt, K.; Mohebi, B.; Dahl, M.; Bergan, S.; Åsberg, A.; Christensen, H. The influence of CYP3A, PPARα, and POR genetic variants on the pharmacokinetics of tacrolimus and cyclosporine in renal transplant recipients. *Eur. J. Clin. Pharmacol.* 2004, 70, 685–693. [CrossRef]
17. Madsen, M.J.; Bergmann, T.K.; Brossen, K.; Thiessson, H.C. The pharmacogenetics of tacrolimus in corticosteroid-sparse pediatric and adult kidney transplant recipients. *Drugs R&D* 2017, 17, 279–286.
18. De Jonge, H.; Metalidis, C.; Naessens, M.; Lambrechts, D.; Kuypers, D.R. The P450 oxidoreductase* 28 SNP is associated with low initial tacrolimus exposure and increased dose requirements in CYP3A5-expressing renal recipients. *Pharmacogenomics* 2011, 12, 1281–1291. [CrossRef]
19. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, n71. [CrossRef]
20. Wells, G.A.; Shea, B.; O’Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. 2002. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 4 January 2022).
21. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. **BMC Med. Res. Methodol.** 2014, 14, 135. [CrossRef] [PubMed]

22. Higgins, J.P.; White, I.R.; Anzueto-Cabrera, J. Meta-analysis of skewed data: Combining results reported on log-transformed or raw scales. **Stat. Med.** 2008, 27, 6072–6092. [CrossRef]

23. Higgins, J.P.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. **Stat. Med.** 2002, 21, 1539–1558. [CrossRef] [PubMed]

24. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. **Biometrics** 1994, 50, 1088–1101. [CrossRef] [PubMed]

25. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. **BMJ** 1997, 315, 629–634. [CrossRef]

26. Elens, L.; Hesselink, D.A.; Bouamar, R.; Budde, K.; De Fijter, J.W.; De Meyer, M.; Mourad, M.; Kuypers, D.R.; Haufroid, V.; Van Gelder, T.; et al. Impact of POR*28 on the Pharmacokinetics of Tacrolimus and Cyclosporine A in Renal Transplant Patients. **Ther. Drug Monit.** 2014, 36, 71–79. [CrossRef] [PubMed]

27. Kurzawski, M.; Malinowski, D.; Dziewanowski, K.; Drozdzik, M. Impact of PPARA and POR polymorphisms on tacrolimus pharmacokinetics and new-onset diabetes in kidney transplant recipients. **Pharm. Genom.** 2014, 24, 397–400. [CrossRef]

28. Li, C-J.; Li, L.; Lin, L.; Jiang, H-X.; Zhong, Z-Y.; Li, W-M.; Zhang, Y-J.; Zheng, P.; Tan, X-H.; Zhou, L. Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR Genetic Polymorphisms on Tacrolimus Metabolism in Chinese Renal Transplant Recipients. **PLoS ONE** 2014, 9, e86206. [CrossRef] [PubMed]

29. Zhang, J.J.; Liu, S.B.; Xue, L.; Ding, X.L.; Zhang, H.; Miao, L.Y. The genetic polymorphisms of POR* 28 and CYP3A5* 3 significantly influence the pharmacokinetics of tacrolimus in Chinese renal transplant recipients. **Int. J. Clin. Pharmacol. Ther.** 2015, 53, 728–736. [CrossRef] [PubMed]

30. Liu, S.; Chen, R.X.; Li, J.; Zhang, Y.; Wang, X.D.; Fu, Q.; Chen, L.; Liu, X.; Huang, H.; Huang, M.; et al. The POR rs1057868–rs2868177 GC-GT diplotype is associated with high tacrolimus concentrations in early post-renal transplant recipients. **Acta Pharmacol. Sin.** 2016, 37, 1251–1258. [CrossRef] [PubMed]

31. Phupradit, A.; Vadcharavivad, S.; Insathan, A.; Kantachavesiri, S.; Areepium, N.; Sra-Ium, S.; Aumanno, T.; Sukasem, C.; Sumethkul, V.; Kitiyakara, C. Impact of POR and CYP3A5 Polymorphisms on Trough Concentration to Dose Ratio of Tacrolimus in the Early Post-Operative Period Following Kidney Transplantation. **Ther. Drug Monit.** 2018, 40, 549–557. [CrossRef] [PubMed]

32. Huang, N.; Agrawal, V.; Giacomini, K.M.; Miller, W.L. Genetics of P450 oxidoreductase: Sequence variation in 842 individuals of four ethnicities and activities of 15 missense mutations. **Proc. Natl. Acad. Sci. USA** 2008, 105, 1733–1738. [CrossRef]

33. Huang, N.; Pandey, A.V.; Agrawal, V.; Reardon, W.; Lapunzina, P.D.; Mowat, D.; Jabs, E.W.; Van Vliet, G.; Sack, J.; Flück, C.E.; et al. Diversity and function of mutations in p450 oxidoreductase in patients with Antley-Bixler syndrome and disordered steroidogenesis. **Ann. J. Hum. Genet.** 2005, 76, 729–749. [CrossRef]

34. Fluck, C.E.; Mullis, P.E.; Pandey, A.V. Reduction in hepatic drug metabolizing CYP3A4 activities caused by P450 oxidoreductase mutations identified in patients with disordered steroid metabolism. **Biochim. Biophys. Res. Commun.** 2010, 401, 149–153. [CrossRef] [PubMed]

35. Agrawal, V.; Choi, J.H.; Giacomini, K.M.; Miller, W.L. Substrate-specific modulation of CYP3A4 activity by genetic variants of cytochrome P450 oxidoreductase. **Pharm. Genom.** 2010, 20, 611–618. [CrossRef] [PubMed]

36. Oneda, B.; Crettol, S.; Sirot, E.J.; Bochud, M.; Ansermot, N.; Eap, C.B. The P450 oxidoreductase genotype is associated with CYP3A activity in vivo as measured by the midazolam phenotyping test. **Pharm. Genom.** 2009, 19, 877–883. [CrossRef] [PubMed]

37. Yang, G.; Fu, Z.; Chen, X.; Yuan, H.; Yang, H.; Huang, Y.; Ouyang, D.; Tan, Z.; Tan, H.; Huang, Z.; et al. Effects of the CYP Oxidoreductase Ala303Val Polymorphism on CYP3A Activity In Vivo: A Randomized, Open-Label, Crossover Study in Healthy Chinese Men. **Clin. Ther.** 2011, 33, 2060–2070. [CrossRef] [PubMed]

38. Kuypers, D.R.; Claes, K.; Evenepoel, P.; Maes, B.; Vanrenterghem, Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. **Clin. Pharmacol. Ther.** 2004, 75, 434–447. [CrossRef] [PubMed]

39. Borobia, A.M.; Romero, I.; Jimenez, C.; Gil, F.; Ramirez, E.; De Gracia, R.; Escuin, F.; González, E.; Sansuán, A.J.C. Trough Tacrolimus Concentrations in the First Week After Kidney Transplantation Are Related to Acute Rejection. **Ther. Drug Monit.** 2009, 31, 436–442. [CrossRef]

40. Gijzen, V.M.; van Schaik, R.H.; Soldin, O.P.; Soldin, S.J.; Nuiman, I.; Koren, G.; de Wildt, S.N. P450 oxidoreductase* 28 (POR* 28) and tacrolimus disposition in pediatric kidney transplant recipients—A pilot study. **Ther. Drug Monit.** 2014, 36, 152–158. [CrossRef] [PubMed]

41. Sherry, S.T.; Ward, M.H.; Kholodov, M.; Baker, J.; Phan, L.; Smigielski, E.M.; Sirotkin, K. dbSNP: The NCBI database of genetic variation. **Nucleic Acids Res.** 2001, 29, 308–311. [CrossRef]