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The effect of POR*28, CYP3A5*3 and their combined genotypes on everolimus pharmacokinetics in renal transplant recipients


Submitted
In our recent article “Effect of CYP3A4*22, CYP3A5*3, and CYP3A Combined Genotypes on Cyclosporine, Everolimus, and Tacrolimus Pharmacokinetics in Renal Transplantation” published in this journal [1] we reported that there is no clinically relevant effect of CYP3A5*3, and CYP3A combined genotypes on everolimus pharmacokinetics.

Recently, relationships between POR polymorphisms and tacrolimus pharmacokinetics in renal transplantation have been reported [2,3]. These publications showed that the POR*28 allele was associated with increased in vivo CYP3A5 activity for tacrolimus metabolism in CYP3A5*1 allele carriers. To investigate whether the effect of POR*28 and the combined effect of POR*28 and CYP3A5*3 had a clinically relevant effect on everolimus pharmacokinetics we genotyped all patients for POR*28. Hepatic microsomal P450 enzymes require P450 oxidoreductase (POR). Polymorphisms in the gene encoding POR have been linked to altered CYP activity and they appear to be substrate specific [4], however this relationship was absent for sirolimus pharmacokinetics [5].

Our stable renal transplant recipient cohort were genotyped for CYP3A5*3 (rs776746) and POR*28 (rs1057868) with Pyrosequencer 96MA (Isogen, IJsselstein, The Netherlands). All allele frequencies were in Hardy–Weinberg equilibrium and distribution corresponded with previous findings [2,3,5]. Univariate covariate analysis using population pharmacokinetic methodology showed no significant association between apparent everolimus clearance and POR*28, CYP3A5*3 nor POR*28 & CYP3A5*3 combined. Clinically irrelevant trends were observed for POR*28 (-4% for *28 allele carriers vs non-carriers), CYP3A5*3 (+12% for *1 allele carriers vs non-carriers) and their combination (+11% for *1 allele carriers of CYP3A5*3 with at least one *28 allele of POR vs non-carriers). Moreover, high variability was seen within the genotype groups as shown in Figure 1. In contrast to what was found for tacrolimus by Elens et al. and de Jonge et al. [2,3] CYP3A5*1 allele carriers that were carriers of at least 1 POR*28 allele showed no clinically relevant effect on everolimus pharmacokinetics. Our results are similar to what was found for sirolimus by Woillard et al. [5]. In summary these data show that in contrast to tacrolimus but just like sirolimus, POR*28, or the combination of combination of POR*28 & CYP3A5*3 appears not to be suitable as a biomarker to improve prediction of everolimus exposure in renal transplantation recipients on everolimus and prednisolone duo therapy.
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Figure 1: Box plots representing the average everolimus apparent clearance (L/hour) of the different genotype groups with error bars and the number of patients in each group. POR (*1/*1 = POR*28 non-carriers, *1/*28 or *28/*28 = POR*28 carriers, NG = not genotyped), CYP3A5 (*1/*3 or *1/*1 = CYP3A5*1 carriers, *3/*3 = CYP3A5*1 non-carriers, NG = not genotyped), and POR & CYP3A5 combined: (C1: CYP3A5*3/*3 and POR*1/*1 or POR*1/*28, C2: CYP3A5*3/*3 and POR*28/*28, C3: CYP3A5*1/*1 or CYP3A5*1/*3 and POR*1/*1, and C4: CYP3A5*1/*1 or CYP3A5*1/*3 and POR*1/*28 or POR*28/*28, NG = not genotyped). Apparent clearance was calculated using the base model.
References


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