Pharmacogenetics in Chronic Kidney Disease

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Contributor: Maria Tziastoudi

Chronic kidney disease (CKD) is an important global public health problem due to its high prevalence and morbidity. Although the treatment of nephrology patients has changed considerably, ineffectiveness and side effects of medications represent a major issue. Pharmacogenetics could fill this gap.

Keywords: genetic association ; chronic kidney disease ; meta-analysis ; pharmacogenetics

1. Introduction

Chronic kidney disease (CKD) continues to constitute a global health burden. It is known that CKD elevates the risk of cardiovascular disease, kidney failure, and other complications [1][2][3]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification, CKD is defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for 3 months or more, irrespective of the cause [4]. Although significant progress has been made in the treatment of nephrology patients with both conservative therapies and dialysis or transplantation, the emergence of drug-related problems such as ineffectiveness and side effects represents a major issue [5]. Pharmacogenetics could fill this gap [6].

Over the last 30 years, new drugs have been introduced to treat major kidney diseases, slow down the progression of CKD, and reduce the development of clinical complications associated with dialysis and kidney transplantation [7]. The use of different combinations of potent immunosuppressive drugs in transplant patients (calcineurin inhibitors, mammalian target of rapamycin inhibitors (mTORs), corticosteroids) have significantly improved the treatment of various renal disorders, and the short- and long-term pharmacological management of renal graft recipients [8].

In general, currently approved immunosuppressive drugs for maintenance therapy include calcineurin inhibitors (cyclosporine (CsA), tacrolimus (TAC)), mTOR inhibitors (sirolimus (SIR), everolimus), antiproliferatives (azathioprine (AZA) and mycophenolic acid (MPA)) and biologic drugs (belatacept) [9]. Differences between individuals regarding the efficacy and safety of immunosuppressive treatment are determined to some extent by genetic factors. For example, a common nonfunctional splicing variant, CYP3A5*3 (rs776746), determines TAC doses [10]. More specifically, patients with the CYP3A5*3/*3 genotype require less TAC to reach target concentrations compared with cytochrome P450 family 3 subfamily A member 5 (CYP3A5) CYP3A5*1 allele carriers [11]. Tacrolimus pharmacokinetic and pharmacodynamic variability is also attributed to ATP binding cassette subfamily B member 1 (*ABCB1*) variants: 1236C > T (rs1128503), 2677G > T/A (rs2032582), and 3435C > T (rs1045642) [12][13]. In addition, another example of the implication of pharmacogenetics in nephrology constitutes the thiopurine S-methyltransferase (*TPMT*) gene [14]. Many lines of evidence have reported that genetic variants located in the TPMT gene affect AZA metabolism and patients with low activity (10% prevalence) or absent activity (0.3% prevalence) are at risk of myelosuppression [15][16]. Among 20 variant alleles (*TPMT* *2-*18) identified to date, mutant alleles *TPMT*2 and TPMT*3 explain more than 95% of defective gene activity [8][17].

2. Pharmacogenetic Studies in Patients with Chronic Kidney Disease

With regard to the *ABCB1* gene and the three polymorphisms harbored in it, the *ABCB1* 1236 C > T polymorphism was statistically significant in the studies with prednisolone (PRE) and mycophenolate (MMF). The *ABCB1* 2677 G > T polymorphism was also statistically significant in the analyses for PRE, whereas the *ABCB1* 3435 C > T polymorphism was statistically significant in the analyses for MMF and cyclosporine (CsA).

Regarding the genes encoding interleukins, the *IL-10* -592 C > A polymorphism in all genetic models and --819 C > T in the dominant and the additive model in the CsA analyses were statistically significant. Another statistically significant polymorphism was the ITPA 94 C > A polymorphism in the recessive model in azathioprine (AZA) analyses. In addition, a statistically significant polymorphism was the *MIF* -173 G > C polymorphism in PRE analyses in all genetic models. Statistically significant results were also obtained for the *TNF*-308 G > A polymorphism in the recessive and additive models in PRE analyses.

Regarding heterogeneity control, statistically significant heterogeneity was observed among the studies regarding the *CYP2C19**2 polymorphism in the main analysis for cyclophosphamide (CYC): for the TPMT 1 vs. polymorphism, 3C, *MIF* -173 G > C, *Il-6* C-174G for PRE; for *TPMT* 1 vs. polymorphisms, 3C, *ABCB1* 1236 C > T, 2677 G > T, for CsA; for *TPMT* 1 vs. polymorphism 3C for AZA. For tacrolimus (TAC), a statistically significant heterogeneity was observed for polymorphisms *ABCB1* 2677 G > T and 3435C > T. Due to the statistically significant heterogeneity, the above results should be interpreted with caution, the majority of which are non-statistically significant.

Variants *ABCB1* (1236 C > T, 2677 G > T, 3435 C > T), *IL-10* (-592 C > A, -819 C > T), *ITPA* (94 C > A), *MIF* (-173 G > C), and *TNF* (-308 G > A) gave significant results, suggesting the contribution of these loci to different responses to treatment in patients with CKD.

However, only *TPMT* has been included in the table of pharmacogenetics biomarkers in drug labeling of the U.S. Food and Drug administration (FDA) for the treatment of AZA [18]. More specifically, homozygous *TPMT*-deficient patients experience severe myelosuppression. For the other variants, the results are not so robust.

Regarding calcineurin inhibitors, the effects of *ABCB1* 3435C > T, 1236C > T, and 2677G > T/A SNPs on the pharmacokinetics of CsA and TAC remain uncertain, with conflicting results. Genetic linkage between these three genotypes suggests that the pharmacokinetic effects are complex and unrelated to any *ABCB1* polymorphism. In contrast, it is possible that these polymorphisms may exert a small but combined effect. Any effect is likely to be in addition to the effects of *CYP3A5* 6986A > G SNP [12].

With regard to the *CYP3A5* 6986A > G variant, eight studies [19][20][21][22][23][24][25][26] included patients under treatment with pulse CYC, steroids, calcineurin inhibitors, and AZA/SIR. In contrast to CsA, a strong relationship between the CYP3A5 6986A > G SNP and TAC pharmacokinetics was demonstrated in kidney, heart, and liver transplant recipients, as well as in healthy volunteers [12]. Several recent studies have reported an approximate halving of the TAC C_0/dose and doubling of the tacrolimus dose requirements in *CYP3A5* expressers compared to that in *CYP3A5* non-expressers [27][25][28][29][30][31][32].

However, studies with a small number of patients may be responsible for many conflicting results to date. The low frequency of some alleles, such as *CYP3A4**1B allele, may not have been sufficient in many cases to detect a difference. In addition, the influence of ethnicity may play a role, as mutated genotypes are often more common in specific ethnic groups. However, even in the same ethnic group, for example in Caucasians, the frequencies of the studied polymorphisms differ. For instance, Caucasians present a minor allelic frequency around 50% regarding the *ABCB1* 1236C > T polymorphism, whereas the studied *TPMT* allele frequency polymorphisms range from 0.2–5.5% in Caucasians. Although the genotype itself, rather than the underlying ethnicity, should theoretically detect any differences, it is possible that indeterminate genetic differences (for example, co-inherited SNPs) among Africans, Caucasians, and Asians contribute to significant variables. In addition, the associations presented in these meta-analyses resulted from pooling a relatively small number of studies and patients with large heterogeneity between studies. Furthermore, the impact of effect modifiers such as age and the pre-treatment cytogenetic and molecular genetic findings was not considered as the individual studies did not provide the relevant data. Indeed, we have not included the analyses of interactions of age and comorbidity in the meta-analysis because these details were not included in the available data. It would be very interesting if future pharmacogenetic studies included this type of data in the analysis. The present systematic review and meta-analysis included studies that varied in terms of treatment and primary cause of CKD, as well as racial descent. Thus, the results should be interpreted with caution. Future studies with more homogenous studies will shed light on the pharmacogenetics in CKD. Thus, lack of significant association in the remaining gene variants does not exclude the possibility of an association.

Last but not least, epigenetic changes in drug metabolizing enzymes, nuclear receptors, and transporters are associated with individual drug responses and acquired multidrug resistance [33]. Consequently, pharmacoepigenetics could provide an explanation for why patients with the same genotype respond differently to therapy with a specific medication. Unrelated to epigenetics, inflammation can significantly influence the extent of CYP suppression, thus contributing to intra- and interindividual variability to drug exposure [34].

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