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Meta-analysis reveals a lack of association between MRP2 C-24T genetic polymorphism and the pharmacokinetics of mycophenolic acid in adult renal transplant recipients

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ABSTRACT

Background: Recent studies have shown that the multidrug resistance protein 2 (MRP2) C-24T genetic polymorphism is associated with the pharmacokinetics (PKs) of mycophenolic acid (MPA) in renal transplant recipients. However, published studies have reported inconsistent results. Therefore, a meta-analysis and systematic review were conducted to evaluate the effect of the MRP2 C-24T polymorphism on the PKs and safety of MPA in the literature.

Methods: A comprehensive literature search was performed using the PubMed, Cochrane Library and Embase databases. Heterogeneity was assessed; forest plots were also used. In total, 10 studies with 1048 renal transplant recipients were included in our meta-analysis and systematic review.

Results: The results showed that the MRP2 C-24T polymorphism was not associated with the PKs of MPA [AUC_{0-12}/dose: SMD = −0.103 (−0.566, 0.361), $P = 0.143$] using the dominant model in our analysis, and a lack of correlation was found between the C-24T polymorphism and the occurrence of biopsy-proven acute rejection (BPAR) or MPA-related adverse events in the systematic review.

Conclusions: In conclusion, our meta-analysis and systematic review suggest that the MRP2 C-24T polymorphism has no significant effect on the PKs of MPA in steady-state conditions and is not associated with the safety of MPA in adult renal transplant recipients. Moreover, further large-scale, case-control studies with rigorous designs should be carried out to confirm these conclusions.

Contents

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1. Introduction

Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), which have been widely used for renal transplant recipients (Halloran et al., 1997; Irish et al., 2010), is a selective inhibitor of inosine monophosphate dehydrogenase (IMPDH), is involved in de novo nucleotide biosynthesis, and blocks B and T lymphocyte proliferation (Allison and Eugui, 2000).

Upon reaching the systemic circulation, MMF is rapidly converted to MPA by serum esterases; in contrast to MMF, EC-MPS remains intact in the stomach. However, once in the small intestine (a nonacidic environment) MPA is released (Arns et al., 2005; Meier-Kriesche et al., 2000). After absorption, MPA is extensively bound to serum albumin and is mainly metabolized to its primary inactive forms, MPA-phenyl-glucuronide (MPAG) and MPA-acyl-glucuronide (AcMPAG), by glucuronyl transferases (UGTs) in the liver (Rosso Felipe et al., 2009). Inactive MPAG and AcMPAG are transported into hepatocytes by organic anion-transporting polypeptides (OATP; gene symbol: SLCO) (Picard et al., 2010). Then, MPAG and AcMPAG are excreted into the bile via the canalicular export pump multidrug resistance protein 2 (MRP2; gene symbol: ABCC2). After these metabolites are excreted into bile, they are deconjugated into MPA in the gut and further reabsorbed, undergoing the process of enterohepatic circulation (EHC), which accounts for approximately 40% of MPA exposure and which leads to a second plasma peak of MPA at 4 to 12 h after administration (Bullingham et al., 1998; Jiao et al., 2008; Staatz and Tett, 2007).

Studies on the pharmacokinetics (PKs) of MPA showed a potential magnificent association with polymorphisms of genes encoding drug-metabolizing enzymes (such as UGTs) and transporters (such as OATP and MRP2), which may provide useful clinical measurements for individualizing MPA therapy based on the genotype (Bernard et al., 2006; Kagaya et al., 2007; de Jonge and Kuypers, 2008; Jirasiritham et al., 2004; Brunet et al., 2006). In addition, >50% of renal transplant recipients suffer from adverse events related to MPA, including gastrointestinal symptoms, hematotoxicity and infections (Staatz and Tett, 2007; Knoll et al., 2003). More importantly, these dose-dependent MPA-related adverse events could be relieved by decreasing the dose of MPA, which is offset by an increased risk of biopsy-proven acute rejection (BPAR) (Knoll et al., 2003). Thus, considering the clinical PKs and safety of MPA, individualization of MPA therapy by therapeutic drug monitoring is not easily conducted according to routine clinical practice. However, whether these single nucleotide polymorphisms (SNPs) could predict and guide MPA therapy individually in renal transplant recipients remains to be evaluated.

MRP2, a main transporter involved in MPAG excretion, is encoded by a gene located on chromosome 10q24. This organic anion transporter is primarily expressed on the luminal membrane of proximal renal tubular cells and the apical membrane of hepatocytes, as well as in epithelial cells of the intestine, the placenta and the blood-brain barrier (Schaub et al., 1999; Dietrich et al., 2003; Masereeuw et al., 2003). The C-24T SNP in the MRP2 5′-UTR region, which happens to be a relatively high allelic frequency (18%), is reported to be relevant to the expression of irinotecan (CPT-11) in cancer patients (Suzuki and Sugiyama, 2002; Ito et al., 2001; Zhou et al., 2005). However, the effect of C-24T SNP on the PKs of MPA exposure is controversial.Naesens et al. (2006) observed that the MRP2 C-24T polymorphism is associated with a lower oral clearance of MPA in recipients with stable allograft function. In contrast, results from several studies showed no significant association between C-24T SNP and the PKs of MPA in steady-stable conditions (Baldelli et al., 2007; Geng et al., 2012). Therefore, our meta-analysis and systematic review aimed to evaluate the influence of the MRP2 C-24T genetic polymorphism on the PKs and safety of MPA in adult renal transplant recipients.

2. Methods

2.1. Literature search

A comprehensive search was conducted in PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Embase (updated on November 1st, 2015) to identify all potentially relevant studies by two independent authors (Liu K and Liu XZ). The following search items were used: (Mesh items, “kidney transplantation”), and (“genetic polymorphisms” or “single nucleotide polymorphism” or “SNP” or “gene mutation” or “genetic variants”), and (“mycophenolate mofetil” or “MMF” or “mycophenolic acid” or “MPA” or “enteric-coated mycophenolate sodium” or “EC-MPS” or “CellCept” or “Myfortic”), and (“multidrug resistance-association protein 2” or “MRP2” or “ATP-Binding Cassette Sub-Family C Member 2” or “ABCC2”), and (“C-24T” or “-24C>T”). Furthermore, the reference lists of all studies that were included in the meta-analysis and the abstracts of annual meetings of the American Society of Nephrology, the International Transplant Society and the European Dialysis and Transplantation Association were reviewed.

2.2. Study selection

To include relevant studies in this review, the following criteria were used: (Halloran et al., 1997) a case-control or cohort study that was designed to investigate the influence of the specific gene polymorphism MRP2/ABCC2 C-24T on the PKs of MPA or on adverse events of MPA administration in de novo or secondary renal transplant recipients (Irish et al., 2010); MPA blood trough concentrations or AUCs were measured separately in subjects with three different genotypes or separately in CC and CT + TT genotypes; and (Allison and Eugui, 2000) the presence of at least one outcome of interest for our study. According to the above criteria, two authors (Liu K and Liu XZ) assessed and selected trials for the final analysis independently, with divergences resolved by consensus.

2.3. Data extraction and quality assessment

Relevant data from all eligible studies were extracted independently by two reviewers (Liu XZ and Wang ZJ), and discrepancies in the data extraction were resolved through consensus. The following information was collected: first author, ethnicity, publication years, study design, demographic data, immunosuppressive protocol, MMF or EC-MPS dosage, MPA concentration and MRP2 C-24T genotype measurement methods, genotype frequency, post-transplantation time, MPA area under curve$_{0-12}$ (AUC_{0-12}), dose-adjusted MPA AUC_{0-12} (MPA AUC_{0-12}/dose) and dose-adjusted C_0 (C_0/dose). For continuous data, information was collected as the mean (SD). If the data were expressed as subjects with three different genotypes, a statistical method reported from the Cochrane Handbook (Higgins and Green, 2008) was employed to estimate the mean (SD).

The quality of all eligible studies was evaluated by two independent reviewers (Liu XZ and Wang ZJ) through a checklist derived from the Newcastle-Ottawa Scale (NOS), which contained 8 items and assigned a quality score that ranged from 0 to 9 points. Studies with >7 points were considered of high quality (Stang, 2010).

2.4. Statistical analysis

The pooled data were used to assess the strength of the association between genotypes and the PKs of MPA by the standard mean difference (SMD) with 95% confidence intervals (95% CIs). A p value < 0.05 was considered statistically significant. Heterogeneity among trials was determined by I^2, which was defined as 100% * (Q − df) / Q, where Q is Cochran's heterogeneity statistic