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Review Article
Cyclosporine Transporter Pharmacogenomic Effect in Transplantation: An Updated Systematic Review

[1]Muhannad Faleh Alanazi and [2]Gomaa Mostafa-Hedeab

[1]Division of Radiology, Department of Internal Medicine, College of Medicine, Jouf University, Sakaka 72388, Kingdom of Saudi Arabia
[2]Department of Pharmacology, Medical College, Jouf University, Sakaka 72388, Kingdom of Saudi Arabia

Abstract

Cyclosporine (CsA) is commonly used in organ transplantation based on its immunosuppressant activity. Monitoring CsA fluctuation in the blood level is important as it belongs to drugs with narrow safety margin windows. Its low level may result in loss of immunosuppressant activity leading to rejection. In contrast, a high CsA level may result in CsA-related adverse effects. The CsA absorption is controlled mainly by *ABCB1* and *ABCB2* transporters. The current study aims to investigate the gene controlling CsA absorption among transplanted patients. A literature review was conducted from January, 2000 to November, 2024 using Scopus, Embase, as well as PubMed bibliography. The research focuses on cyclosporine, transplantation, pharmacogenetics and pharmacogenomics. The current research items were met by 482 which were subjected to the exclusion of duplication or unfit research papers that resulted in 48 final research papers, which were then analyzed. Hence, found a strong association between some *ABCB1* gene polymorphisms and CsA blood level, while some results nullify that. These findings necessitate the need for a genome-wide association study with multi-centers with different ethnicities for better understanding and accurate conclusions of the CsA dosing based on genetic variability.

Key words: Cyclosporine, transporter, transplantation, pharmacogenomics, genome-wide association

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Corresponding Author: Gomaa Mostafa-Hedeab, Department of Pharmacology, Medical College, Jouf University, Sakaka 72388, Kingdom of Saudi Arabia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The success of CsA isolation from fungus *Tolypocladium inflatum* gams soil samples in 1976, a neutral lipophilic character, was considered an important event in drug discovery. Cyclosporine A (CsA) and cyclosporine C (CsC) were the only metabolites that showed pharmacologic activities. The CsA is the only one that produced a favorable immunosuppression activity in addition to its anti-parasitic, fungicidal and anti-inflammatory effects[1]. In 1983, the Food and Drug Administration (FDA) approved its use as an immunosuppressant agent and then widely used after the transplantation of almost all organs[2].

Resulting in a reduction of morbidity, rejection episodes and decreased transplanted recipients hospitalization days in transplant recipients, as well as increased quality of life and survival[3]. The CsA is effectively used as an immunosuppressive agent in the treatment of many diseases such as uveitis, psoriasis as well as nephrotic syndrome[4]. In addition; CsA effectively alleviates dry eye[5].

The CsA action is mediated through its binding to cyclophilin of T-cell to form CsA/cyclophilin, resulting in inhibition of IL-2, IL-4 and of nuclear factor of activated T cells via its dephosphorylations[6-8], reflected in a marked reduction of effector T-cell[9]. In addition; it decreases IL-1, IL-6 and TNF-α levels as well[10].

The CsA showed limited and high variability in its absorption[11]. Its physical character is a hydrophobic cyclic peptide, making its oral absorption incomplete and the presence of bile acids for its emulsification is essential for its absorption[12]. The development of microemulsion formulations widely improves its absorption rate independent of bile acid[13]. The CsA monitoring is essential[14], as it has a narrow therapeutic index with variability in drug level among persons[15].

In the early phase post-transplantation, patients, CsA variability may reach up to six-fold differences among these patients[16]. The importance of this finding to be considered is the variation in the CsA level in this stage is dangerous, where hypo-immunosuppressant results in rejection that may reach up to a fourfold increase than normal[17].

The CsA is a substrate of CYP3A and P-Glycoprotein (P-gp)[18], both of these enzymes reduce the rate of CsA absorption in the small intestine[19]. Their combined effect on CsA explained the low CsA bioavailability which ranges from 10 to 50%[20-23]. The Co-administration of any mediation that induces or inhibits CYP3A4 or P-gp can alter CsA levels; Grapefruit juice can increase the levels of CsA[24], through its action on P-gp[25].

The P-gp is highly expressed in many tissues, especially in the intestinal, liver and kidney tissues[15]. It induces the efflux of substrate drugs from the intestinal lumen and increases its bile and urine excretion[18]. The CYP3A4 and CYP3A5 represent the most important members in the CYP3A drug-metabolizing enzymes family; in which CYP3A5 contributes to a larger extent than CYP3A4 in the CsA metabolism[18].

Moreover, CsA absorption and metabolism are different in pediatrics than in adults[26]. This may be related to a time-dependent manner effect of *ABCB1* and *SXR* SNPs of renal transplanted patients from childhood to adulthood periods[27].

The CsA is extensively metabolized by liver CYP3A4 and CYP3A5 enzymes and to a lesser extent in the small intestine and Kidney[28]. Excretion of metabolites into the bile is the major route of drug elimination.

The variation in the liver and intestinal CYP3A and P-gp expression and function may explain the inter-individual variability of CsA blood levels and its metabolites as well[29]. In the same way, the nephrotoxicity susceptibility may be a result of these expression levels that determine the extent and level of its metabolite that plays a crucial role in nephrotoxicity individual risk[29].

Although the exact cause of CsA induced-nephrotoxicity is not well elucidated; many reports explored the possible mechanism of this nephrotoxicity; which may be due to the generation of inflammation, oxidative stress (OS)[30,31], reactive oxygen species (ROS) overproduction[30-32], OS autophagy and apoptosis[30], CsA induces lipid peroxidation through an increase in oxidative stress production[33] or via (Transforming Growth-Factor-β1) TGF-1β production.

Moreover; CsA increases inflammatory-induced fibrosis and kidney failure[34] which is a result of epithelial cell Epithelial-Mesenchymal Transition (EMT) induction leading to its apoptosis and amelioration of DNA synthesis[35]. Finally, it may induce various types of vasoconstrictor agents[36] and osteopontin to renal tissues[37].

The objective of this updated systematic review is to evaluate the pharmacogenomic effects of cyclosporine transporters in transplantation. It aims to assess how genetic variations in transporter genes influence cyclosporine pharmacokinetics, efficacy and toxicity. The review also seeks to identify potential biomarkers for optimizing immunosuppressive therapy in transplant recipients.

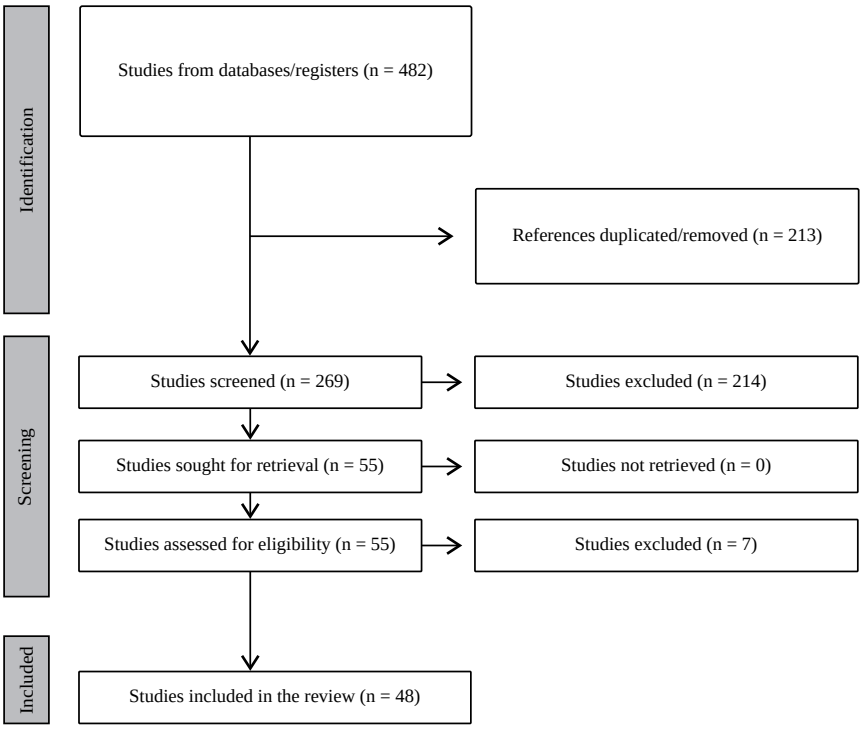

Fig. 1: Flow chart of the included studies

ATP-binding cassette: The membrane transporters known as ATP-binding cassette (ABC) proteins are made up of both transmembrane and nucleotide-binding domains. There are about fifty ABC transporters known to exist in humans[38]. These proteins are crucial transporters of ions, chemical compounds, peptides, lipids and medications and they have a wide range of functions in human physiology. Additionally, they have been linked to several illnesses and pathological situations, including medication resistance in the case of P-Glycoprotein (P-gp) and cystic fibrosis[39].

Although these transporters carry out a variety of functions, drug efflux is the main way that they contribute to drug distribution. The P-gp is a well-known member of the ABCB subgroup within the ABC family. Because it is expressed in the kidneys[40], the intestine[41] and among other places, it plays a role in the distribution and removal of therapeutic drugs.

The ABC transporter family also includes *ABCG2*, occasionally referred to as Breast Cancer Resistance Protein (BCRP). It transports many medications, including conjugates, as well as metabolites and uric acid. Additionally, extracellular, transmembrane and intracellular components make up BCRP's structure[42]. The transporter's existence is linked to chemoresistance in breast cancer tumors[43], especially metastatic lesions[44], as the name implies. The kidneys, gastrointestinal tract and placenta are among the tissues that express the transporter[45].

The expression and functionality of these transporters influence the bioavailability and removal of therapeutic targets. The ABC proteins participate in drug transport and are expressed in the kidneys, gut and blood-brain barrier. Recently the effects of different circumstances on ABC transporters. The P-gp, sometimes referred to as *ABCB1*, transports a variety of medications, such as peptide drugs[46], immunosuppressants[47], natural agents[48] and cardiovascular drugs[49].

Thus, although the development of CsA formulations which is markedly improved its absorption; the variation in the liver and intestinal CYP3A and P-gp expression and function may explain the inter-individual variability of CsA blood levels and its metabolites as well. The lack of an international clinical guideline incorporating pharmacogenomic reports, especially P-gp and CYP3A expressions, interferes with CsA personalization.

Research methodology: A literature review was done from January, 2000 till November, 2024 using three bibliographic databases: Embase, PubMed and Scopus. The search term was: "Cyclosporine", "Transplantation", "Pharmacogenetics" and "Pharmacogenomics". The summary of the PRISMA is demonstrated in Fig. 1; among 482 research papers, only 48 were included in the final review screening.

Association between *ABCB1* gene polymorphisms on CsA kinetic and effect: Many studies explored the impact of *MDR1* (*ABCB1*) polymorphisms among different types of transplanted patients. The results were conflicting. The main output of the *ABCB1* effect on CsA is summarized in Table 1.

Some authors found no association between *ABCB1* gene polymorphisms with the pharmacokinetics of CsA[50,51], while others proved its minor effect on CsA kinetic[52] where functional G1199A rs2229109 polymorphism showed a superior effect compared to the non functional C3435T.

On the other hand, Grenda *et al.*[53] a study involving 197 renal-stable transplanted patients stated that *MDR1* polymorphisms affect only the first post-transplant week CsA difference among transplanted recipients.

In a study of 197 stable renal transplant patients in the United Kingdom; the targeted CsA blood concentrations strategy can't be based on *MDR1* haplotypes as it may have a minor role in determining CsA kinetics[54].

While some studies showed a strong association between *MDR1* (*ABCB1*) polymorphisms and CsA pharmacokinetics[55-57].

Among recent renal transplanted Chinese patients receiving diltiazem, *MDR1* C1236T; rs1128503 G2677T/A SNP or haplotypes C-G-C, T-G-T and T-T-C are found to be associated with CsA concertation 58, previous results were also confirmed by Contreras-Castillo *et al.*[58].

Lastly, *ABCB1* SNPs were found to affect CsA in renal transplanted patients in a time-dependent manner during development from childhood to adulthood[27], it may have an impact on CsA personalized medicine to individualize CsA doses among Allogeneic hematopoietic cell transplantation[59].

On the other hand, many studies concluded other related effects associated with *ABCB1* SNPs. Foote *et al.*[60] showed *ABCB1* SNPs P-gp important role in renal transplant recipients' peripheral blood lymphocytes CD3(+); interestingly P-gp activity was influenced by CsA but macrolide exposure has no role while, Fredericks *et al.*[61] concluded that, the *ABCB1* polymorphism has an age-related effect on oral bioavailability in 104 Swedish pediatric patients before renal transplantation patients.

Additionally, Foote *et al.*[62] showed that *ABCB1* 3435C>T rs1045642 could be used in the detection of some CsA-related side effects in renal transplant recipients *ABCB1* 3435C>T rs1045642 and 2677G>T rs2032582 polymorphisms which agree with the results of Sun *et al.*[59]. Similarly, the *ABCB1* 2677 GG may give bases for CsA personalized medicine as well as allograft outcomes in transplanted patients[63]. Finally; another study by Wang *et al.*[64] identifies the correlations between *ABCB1* rs1128503, CC genotype and infection susceptibility risk.

Association between *ABCC2* gene polymorphisms on CsA kinetic and effect: The association between *ABCC2* gene polymorphisms showed no significant association between the studied SNPs and CsA levels. Wang *et al.*[65] showed no association between rs717620, rs1885301, rs1128503, rs2032582 or rs1045642 and CsA in a study that included 34 Korean Hematopoietic Stem Cell Transplant Patients. Fanta *et al.*[68] stated no association for an age-related effect of *ABCB1* polymorphism on oral bioavailability, after screening 24C>T rs717620, -129T>C rs3213619, 1554+24T>C rs2235033, 1725+38G>A rs2235013, 1199G>A rs2229109, 1236C>T rs1128503, 1446C>G rs11364609424, C>T rs717620 and 1446C>G rs113646094 among 104 Sweden Pediatric patients before renal transplantation patients. In the same way, the results of Sánchez-Lázaro *et al.*[71], who screened 1249G>A rs2273697, 3972C>T rs3740066, -24C>T rs717620 among 60 (36 on CsA) Spanish Heart transplant patients treated patients[64].

On the other hand, Zgheib *et al.*[66] concluded a strong association in a study of 68 Croatia recipient-donor pairs. They investigated 24C>T rs717620 and 1249G>A rs2273697 donors' *ABCC2* 1249G>A polymorphism concluded an increased clearance and reduced exposure by attenuating gut, the liver and the kidney *MRP2*; they stated the effect of *ABCC2* 1249 G>A differs in donors than recipients. Where it induces the renal CsA effect among donors while improving the liver and the gut CsA among recipients[66].

The association of the *ABCB2* gene polymorphism with CsA kinetics, efficacy or adverse effects was summarized in Table 2.

The current review highlighted the importance of transporters pharmacogenomic on CsA personalized therapy among the transplanted recipients. The study perspective was to better CsA dose adjustment and improving transplanted outcomes. One of the current review recommendations is regular pharmacogenomic screening in clinical practice for better CsA therapy justification. Genetic polymorphisms' impact on CsA appears to be significant and may aid in the appropriate pre-transplant CsA dose adjustment. This review may be limited by the absence of multicenter, wide-genome studies with a substantial number of patients from various ethnic backgrounds.

Table 1: *ABCB1* gene polymorphisms association with CsA kinetic, efficacy or adverse effects among transplanted patients

Gene	Var. type	SNP references	Allele	Patient number	Patients type	Country	Clinical implication	Date	References
MDR1 (*ABCB1*)	C3435T 2677G>T>A C1236T T129C	rs1045642 rs2032582 rs1128503 rs3213619	C>T G>T>A C>T T-129C	Seventy (30 CsA)	Renal transplant recipients	Spain	*ABCB1* SNPs in may determine the peripheral CD3(+) blood lymphocytes in renal transplant recipients' CsA may affect P-gp activity exposure	2013	Foote *et al.*[60]
MDR1 (*ABCB1*)	1236C>T G2677T C3435T	rs1128503 rs2032582 rs1045642	C>T A>G, T C>T	21	Allogeneic hematopoietic SCT recipients	Japan	CsA concentration was significantly higher when the genotype of CYP3A5 rs15524 was T/T or rs776746 was G/G	2011	Algharably *et al.*[50]
MDR1 (*ABCB1*)	1236C>T 2677G>T/A	rs1128503 rs2032582	C>T G>T>A	34	Hematopoietic stem cell Transplant	Korea	None of the genetic polymorphisms in *ABCB1* were significant covariates in the pharmacokinetics of CsA	2015	Wang *et al.*[65]
MDR1 (*ABCB1*)	C3435T G1199A	rs1045642 rs2229109	C>T G>A	40	Renal transplanted Patients Renal transplanted Patients	Egypt	*ABCB1* may have a minor role in CsA blood level *ABCB1* G1199A has a greater effect compared to *ABCB* C3435T SNP	2013	Turolo *et al.*[52]
MDR1 (*ABCB1*)	1236C>T 2677G>T>A 3435C>T	rs1128503 rs2032582 rs1045642	C>T G>T>A C>T	832	Renal transplant recipients	Czech Republic	No significant correlations between CsA pharmacokinetics *ABCB1* haplotypes influence the risk of acute rejection *ABCB1* allele arrangement plays a more significant role in p-gp regulation than individual polymorphisms *ABCB1* polymorphisms can determine the risk of acute rejection away from CsA pharmacokinetic parameters. The risk of acute rejection determined by *ABCB1* is independent of pharmacokinetic parameters	2008	Llaudó *et al.*[67]
MDR1 (*ABCB1*)	C1236T G2677T/A C3435T IVS21+49	rs128503 rs2032582 rs1045642 rs2032583	C>T G>T>A C>T IVS21+49	87	Teenagers after kidney transplantation	Italy	None of the CsA pharmacokinetic parameters were associated with the *ABCB1* genetic polymorphism	2010	Fanta *et al.*[68]
MDR1 (*ABCB1*)	1199G>A C1236T 2677G>T/A 3435C>T 1446C>G	rs2229109 rs1128503 rs2032582 rs1045642 rs113646094	G>A C>T G>T>A C>T C>G	104	Pediatric patients before renal transplantation	Sweden	Influence of *ABCB1* polymorphisms on CsA oral bioavailability varies with age	2007	Fredericks *et al.*[61]
MDR1 (*ABCB1*)	C3435T	rs1045642	C>T	200	Related toxicity in a cohort of pediatric renal allograft recipients	Poland	No significant association	2009	García *et al.*[69]
MDR1 (*ABCB1*)	C1236T 2677 G>T>A T3435C T-129C	rs128503 rs2032582 rs1045642 rs3213619	C/T G>T>A T/C T/C	33	Kidney transplant patients	Netherlands	No considerable genotype effects on CsA clearance were found for the selected genes	2010	Singh *et al.*[70]
MDR1 (*ABCB1*)	C1236T	rs1128503	C/T	126	Renal transplant patients	China	*MDR1* variants affect CsA adjusted trough level, this effect is more when diltiazem is co-administered	2015	Contreras-Castillo *et al.*[58]
MDR1 (*ABCB1*)	1236	rs1128503	C>T	112	Renal transplant patients	China	*MDR1* G2677T/A SNP, C-G-C, T-G-T and T-T-C haplotypes influence CSA blood level in Chinese renal transplant patients co-treated with diltiazem	2009	von Ahsen *et al.*[57]

Table 1: Continue

Gene	Var. type	SNP references	Allele	Patient number	Patients type	Country	Clinical implication	Date	References
MDR1 (*ABCB1*)	C3435T C1236T 2677G>T>A 1725+38G>A 1554+24T>C 1199G>A T-129C 61A>G	rs1045642 rs1128503 rs2032582 rs2235013 rs2235033 rs2229109 rs3213619 rs9282564	C>T C>T G>T>A G>A T>C G>A T/C A>G	26	Heart Transplantation	Spain	*ABCB1* SNPs affect CsA level only the first 4 months post-transplantation; this effect seems to disappear in the long term	2011	Sánchez-Lázaro *et al.*[71]
MDR1 (*ABCB1*)	1236C>T 3435C>T 2677G>T/A	rs1128503 rs1045642 rs2032582	C>T C>T G>T/A	69	Living donor renal Transplant recipients	Korea	Using the present model to calculate the dose of CsA with *ABCB1* genotyping isn't possible	2012	Božina *et al.*[72]
MDR1 (*ABCB1*)	3435C>T 2677G>T/A 1236C>T	rs1045642 rs2032582 rs1128503	C>T G>T/A C>T	68	Renal transplant recipients	Spain	*ABCB1* polymorphisms may help predict CsA-associated Adverse effects in renal transplant recipients which is independent of CsA blood level Genetic associations are most likely independent of the drugs through blood concentrations	2013	Foote *et al.*[62]
MDR1 (*ABCB1*)	1236C>T 2677G>T/A 3435C>T	rs1128503 rs2032582 rs1045642	C>T G>T/A C>T	150	Renal transplant patients	Brazil	No effect on C0/dose of CSA	2011	Song *et al.*[73]
MDR1 (*ABCB1*)	2677G>T>A	rs2032582	G>T>A	40	Allogeneic hematopoietic cell transplantation (allo-HCT)	Lebanon	*ABCB1* 2677 G>T>A genetic polymorphism may be used as a predictor in CsA-induced nephrotoxicity Pretransplant screening for this genotype may help CsA blood level adjustment optimization	2020	Sun *et al.*[59]
MDR1 (*ABCB1*)	1236C>T 2677G>T/A 3435C>T	rs1128503 rs2032582 rs1045642	C>T G>T/A C>T	155	Renal transplanted patients	North India	Pre-transplant screening of *ABCB1* 2677GG may help in CsA personalized dose adjustment and expect the risk of all graft rejection	2008	Yates *et al.*[63]
MDR1 (*ABCB1*)	3435C>T 2677G>T/A 1236C>T 1199G>A 1725+38G>A 1554+24T>C -129T>C 61A>G 421C>A	rs1045642 rs2032582 rs1128503 rs2229109 rs2235013 rs2235033 rs3213619 rs9282564 rs2231142	C>T G>T/A C>T G>A G>A T>C T>C A>G 421C>A	60 (36 on CsA)	Heart transplant patients treated	Spain	Occurrence of serious infections was associated with *ABCB1* rs1128503 Presence of the CC genotype decreases the infection risk and low CsA blood level Presence of rs9282564 AG is associated with higher CsA blood levels and renal function impairment Presence of rs2066844 CC in *NOD2/CARD15* is associated with a higher graft rejection risk. *NOD2/CARD15*, a gene related to lymphocyte activation	2015	Wang *et al.*[64]
MDR1 (*ABCB1*)	C3435T	rs1045642	C>T	19	Renal transplant patients	USA	*MDR1* C3435T genotype may provide data help to explain the interracial CsA oral bioavailability differences Effort is still needed to identify the CYP3A5/*MDR1* genotype and phenotype relationship	2003	Santoro *et al.*[56]
MDR1 (*ABCB1*)	C3435T G2677T/A	rs1045642 rs2032582	C>T G>T>A	75	Renal transplant patients	Canada	*MDR1* SNPs influence the CsA level, especially in the early post-transplantation period *MDR1* polymorphisms, study and correlation with other factors may help in establishing CsA personalized medicine in renal transplantation	2006	de Luna *et al.*[55]

Table 1: Continue

Gene	Var. type	SNP references	Allele	Patient number	Patients type	Country	Clinical implication	Date	References
MDR1 (*ABCB1*)	C3435T	rs1045642	C>T	124	Stable caucasian renal transplant	Germany	*MDR1* C3435T genotypes do not affect CsA trough level, renal function or acute rejection risk Efficacy in renal transplant recipients	2001	Azarpira *et al.*[74]
MDR1 (*ABCB1*)	C3435T	rs1045642	C>T	88	Renal transplant patients	Iranian	*MDR1* (3435CC) polymorphisms influenced CsA level as well as dose adjustment only in a few days post-renal transplantation	2006	Woodahl *et al.*[75]
MDR1 (*ABCB1*)	C1236T G2677T/A C3435T	rs1128503 rs2032582 rs1045642	C>T G>T>A C>T	197	Stable renal transplanted	UK	*MDR1* haplotypes and CYP3A5*1 genotype have a minor role in CsA pharmacokinetics These minor effects can't be considered in the establishment of CsA pharmacogenetic bases for personalized medicine	2007	Press *et al.*[54]
MDR1 (*ABCB1*)	C3435T C1236 G2677T/A	rs1045642 rs1128503 rs2032582	C>T C1236 G/T/A	139	Renal transplant recipients	Chilean	No significant associations	2021	Woodahl *et al.*[75]
MDR1 (*ABCB1*)	C1236T 2677G>T>A C3435T	rs1128503 rs2032582 rs1045642	C>T G>T>A C>T	521	Renal transplant recipients	China	*CYP3A* genetic factors were varied in different stages after transplantation	2017	Bandur *et al.*[51]
MDR1 (*ABCB1*)	C1236T 2677G>T>A C3435T	rs1128503 rs2032582 rs1045642	C>T G>T>A C>T	15	Pediatric kidney transplant patients	Italy	*ABCB1* and *SXR* SNPs influence CsA levels following renal from childhood to adulthood in a time-dependent manner	2013	Ferraresso *et al.*[27]
MDR1 (*ABCB1*)	G1199A C1236T 2677G>T>A 3435C4T	rs2229109 rs1128503 rs2032582 rs1045642	G/A C>T G>T>A C>T	147	Myeloablative hematopoietic cell transplantation	USA	No correlations between *ABCB1* and CYP3A5 SNPs or the most common *ABCB1* haplotypes and AKI or CKD *ABCB1* 1199G4A showed no LD to other SNPs Adjusting CNIs doses on these genetic bases is of no value in reducing renal injury following myeloablative HCT	2008	Woodahl *et al.*[75]
MDR1 (*ABCB1*)	C3435T 2677G>T>A	rs1045642 rs2032582	C>T G>T>A	69	De novo renal transplant patients	Canada	*MDR1* polymorphisms influence CsA levels only in early post transplantation week G2677T and C3435T SNPs are in linkage disequilibrium	2007	Grenda *et al.*[53]

Table 2: *ABCC2* gene polymorphisms association with CsA kinetic, efficacy or adverse effects among transplanted patients

Gene	Var. type	SNP references	Allele	Patients number	Patients type	Country	Clinical implication	Date	References
ABCC2	-24C>T 1249G>A C1236T 2677G>T/A 3435C>T	rs717620 rs1885301 rs1128503 rs2032582 rs1045642	C>T G>A C>T G/T/A C/T	34	Hematopoietic Stem cell Transplant patients	Korea	None of the genetic polymorphisms in *ABCC2* were significant covariates in the pharmacokinetics of CsA	2018	Wang *et al.*[65]
ABCC2	24C>T 1446C>G 2677G>T/A 1236C>T 1199G>A 1725+38G>A 1554+24T>C -129T>C 61A>G	rs717620 rs113646094 rs2032582 rs1128503 rs2229109 rs2235013 rs2235033 rs3213619 rs9282564	C>T C/G G>T/A C>T G>A G>A T>C T>C A>G	104	Pediatric patients before renal transplantation	Sweden	*ABCC2* polymorphisms have no age-related effect impact on oral bioavailability	2007	Fredericks *et al.*[61]
ABCC2	1249G>A 3972C>T -24C>T	rs2273697 rs3740066 rs717620	1249G>A 3972C>T -24C>T	60 (36 on CsA)	Heart transplant patients treated	Spain	No significant association	2015	Wang *et al.*[64]
ABCC2 *ABCC2*	-24C>T 1249G>A	rs717620 rs2273697	C>T G>A	68	Recipient-donor pairs	Croatia	*ABCC2* 1249G>A has influenced CsA in both donors as well as the recipient: Among donors it increases CsA clearance and reduces exposure through gutMRP2 in the liver and the kidney and enhances the renal CsA effect In recipients, it enhances CsA action in the liver and the gut	2017	Zgheib *et al.*[66]

CONCLUSION

The current review demonstrates an association between *ABCB1* as well as *ABCB2* SNPs and CsA pharmacokinetic, efficacy or related toxicity while some results nullify that. The difference between the conflicting results may be due to the small sample size and different patient ethnicity of the patients included in the studies. The significant correlation between different SNPs and CsA outcomes makes the CsA-tailored personalized therapy based on patient genotyping a promising and reachable target and the need for a genome-wide association study to obtain accurate and final results.

SIGNIFICANCE STATEMENT

The current systematic review screens the relevant studies dealing with the transporter gene polymorphisms involved in the CsA absorption, efficacy or its related adverse reactions among transplanted patients. The most studied genes *ABCB1* (*MDR1*) were associated with significant results in transplanted patients. The results of this review demonstrated the variability of results in this regard, with significant correlations related to many results. This conclusion raised the need for an upcoming large genome-wide association study with multi-centers with different patient ethnicities to better understand the genetic efficacy and personalization of CsA dosing among transplanted patients.

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