Chapter 20

Metabolic Drug Interactions with Immunosuppressants

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Additional information is available at the end of the chapter

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Abstract

Organ transplantation has become a routine clinical practice for patients with end-stage disease of liver, kidney, heart, or lung. Although improved immunosuppressant therapy substantially contributes to the success of transplantation, clinicians continue to face challenges because of wide interindividual variations in blood concentrations resulting in subtherapeutic or supratherapeutic levels. Many undesired side-effects or therapeutic failure of immunosuppressants as a consequence are the results of differences or changes in drug metabolism. Considering genetic and nongenetic factors, such as co-medication, can refine the immunosuppressant therapy, facilitating personalized treatments to individual recipients. This review provides an up-to-date summary of functional polymorphisms of enzymes involved in the metabolism of immunosuppressants with low molecular weight and of the clinical significance of metabolic drug interactions between immunosuppressive agents and other drugs in therapeutic regimens of transplant recipients.

Keywords: drug metabolism, genetic polymorphism, phenoconversion, calcineurin inhibitors, mTOR inhibitors, corticosteroids, inosine monophosphate dehydrogenase inhibitors

1. Introduction

Many undesired side-effects or therapeutic failures of drugs are the results of differences or changes in drug metabolism. A patient's drug metabolizing capacity, highly influenced by genetic variations or alterations in the expression and activities of drug-metabolizing enzymes, can substantially modify the pharmacokinetics of a drug and eventually its efficacy or toxicity [1]. Even if the routine clinical practice applies blood concentration guided dosing,

the interindividual variability in drug metabolism calls for personalized medication primarily for drugs with narrow therapeutic index [2, 3]. The identification of genetic and nongenetic factors that can potentially affect the pharmacokinetics of a particular drug is a prerequisite of tailored pharmacotherapy [4, 5].

2. Genetic and nongenetic variations of drug-metabolizing cytochrome P450 (CYP) enzymes

CYP enzymes are the key players in the metabolism of most drugs; therefore, interindividual and intraindividual variations in CYP activities are of significant importance in clinical practice. The pharmacokinetic variability can divide the population into poor, intermediate, extensive, and ultra-rapid metabolizer phenotypes. The loss-of-function mutations in CYP genes result in permanent poor metabolism, whereas nongenetic (internal or environmental) factors can substantially modify the expression and activities of CYP enzymes, evoking transient poor or extensive/ultra-rapid metabolism [6, 7]. The clinical relevance for many CYP genetic variants, regarding drug efficacy, adverse drug reactions, or dose requirement, has been clearly evidenced [6–9]; however, the heritable genetic polymorphisms are not the only determinant factors in interindividual differences in drug metabolism. CYP genotype determines the potential for the expression of functional or nonfunctional enzymes; and nongenetic host factors (age, sex, and disease states) and environmental factors (nutrition, medication, smoking, and alcohol consumption) can alter the expression and activities of CYP enzymes [10]. Homozygous wild genotype, predicted to be translated to functional CYP enzyme, can be transiently switched into poor or extensive metabolizer phenotype, due to phenoconversion [1, 11]. Consequently, both the CYP genotype and the current CYP expression or activity should be considered for the estimation of a patient's drug-metabolizing capacity.

The prevalence of loss-of-function or gain-of-function alleles is generally 1–10%; however, the distribution of the common CYP variants varies among different ethnic populations. CYP3A enzymes, responsible for the metabolism of approximately 40% of the drugs on the market, including many immunosuppressant agents, display great genetic and nongenetic variations. For CYP3A5, substantial interethnic differences in allelic variants have been demonstrated. The prevalence of *CYP3A5*3* allele (6986A > G), resulting in splicing defect and nonfunctional CYP3A5 protein, is 88–97% in white (Caucasian), 66% in Asian, and 12–35% in African populations; consequently, a higher average proportion of functional CYP3A5 in the total hepatic CYP3A pool is expected in subjects of black origin [7, 12]. On the other hand, the enormous, even more than 100-fold interindividual variability in the expression and activity of CYP3A4 is attributed to nongenetic factors rather than genetic polymorphisms [13]. *CYP3A4*1B* allele, which has a frequency of 3–5% in white populations, but a much higher frequency in African population (50–82%) has been reported to result in increased transcription; however, the clinical significance of *CYP3A4*1B* to CYP3A4 function seems to be doubtful [14, 15]. *CYP3A4*22* allele with the prevalence of 2.5–8% in white and of 4% in Asian populations displays low hepatic CYP3A4 expression and results in decreased CYP3A4 activity [16]. Although the association between *CYP3A4* genotype and pharmacokinetic behavior of CYP3A-substrates has been extensively studied, no clear phenotype-genotype relationship has been described for CYP3A4.

Beside the genetic polymorphisms, one of the major sources of interindividual or intraindividual variability in drug metabolism is concomitant medication and co-morbidities, evoking phenoconversion, notably CYP induction and enzyme inhibition [17]. CYP induction leads to an increase in the expression and activity of CYP enzymes and contributes to the increased elimination of drugs metabolized by the particular enzyme. Several pathways involving the activation of various nuclear receptors (PXR pregnane X receptor, CAR constitutive androstane receptor, and glucocorticoid receptor) have been reported to enhance the transcription of CYP3A genes and to contribute to the complex regulation of CYP3A enzymes by drugs such as rifampicin, phenobarbital, carbamazepine, and synthetic or natural steroids [18–21]. Reduced drug concentration as a consequence of CYP3A induction leads to the lack of the pharmacological effect and drug failure. Phenoconversion converting genotypic extensive metabolism into phenotypic poor metabolism of drugs may occur during inflammation (sterile or infection-induced inflammation). Elevated release of proinflammatory cytokines (IL-6, IL-1β, TNF-α) has been associated with downregulation of several drug-metabolizing CYPs, including CYP3A enzymes. The mechanism of downregulation is the repression of PXR and CAR that are involved in transcriptional regulation of CYP3A expression [22–26]. As a consequence, transient poor metabolizer phenotype is developed, significantly increasing the risk of adverse drug reactions and impacting the clinical outcome [1, 27]. Likewise, co-medication can also give rise to poor metabolism. Several drugs or food components (e.g., bergamottin) are known to inhibit the function of drug-metabolizing CYPs; therefore, the concomitant treatment with a CYP inhibitor is expected to increase the exposure of those pharmacons that are metabolized by the particular enzyme. As a consequence of CYP inhibition, the risk of increased exposure and drug-induced adverse reactions can be anticipated, primarily for drugs with narrow therapeutic index, such as tacrolimus and ciclosporin.

By recognizing individual differences in drug metabolism, personalized drug therapy adjusted to the patient's drug-metabolizing capacity can help to avoid the potential side effects of drugs. The graft and recipient survival are highly influenced by drug-metabolizing capacity of the liver, and it is essential to predict potential drug-drug interactions and to tailor medication at both early and late postoperative periods.

3. Metabolism of immunosuppressants

In recent decades, transplantation (liver, kidney, heart, and lung) has become a routine procedure for patients with end stage disease. Advances in surgical techniques and postoperative therapy have led to increasing numbers of transplantation and extended survival among these patients. The final outcome of transplantation and the long-term graft function have been improved mainly due to the development of potent and specific immunosuppressive drugs. Immunosuppressants efficiently decrease the risk of rejection, blocking the recipient's immune system and protecting the transplanted organ. Because of the narrow therapeutic indexes and increased risk of adverse drug reactions, it is essential to apply personalized immunosuppressive therapy adjusted to patient's drug-metabolizing capacity.

Immunosuppressants are generally classified according to their molecular mode of action; however, in terms of metabolic drug interactions, two main categories must be distinguished

Immunosuppressant	Pharmacology	Adverse effects	Enzymes responsible for the metabolism
Calcineurin inhibitors:			
Ciclosporin	Selective inhibition of T-cell dependent immune response: Calcineurin inhibition, Inhibition of cytokine production	Nephrotoxicity, hepatotoxicity, Hyperlipidaemia, hypertension, Tremor, hyperkalaemia, hypomagnaesemia, Hypertrichosis, gingiva hyperplasia	CYP3A4/5
Tacrolimus	Selective inhibition of T-cell dependent immune response: Calcineurin inhibition, Inhibition of cytokine production	Nephrotoxicity, hypertension, diabetes, cholestasis, diarrhea, Tremor, hyperkalaemia, hypomagnaesemia	CYP3A4/5
mTOR inhibitors:			
Sirolimus	Inhibition of B- and T-cell proliferation	Thrombocytopenia, anaemia, leukopenia, lymphocele, pneumonitis Hyperlipidaemia, Stomatitis aphtosa, wound-healing complications	CYP3A4/5
Everolimus	Inhibition of B- and T-cell proliferation	Thrombocytopenia, anaemia, leukopenia, lymphocele, pneumonia Hyperlipidaemia, hypertonia, wound-healing complications	CYP3A4/5
Purine analogues:			
Azatioprin	Inhibition of purine metabolism	Bone marrow suppression, leukopenia, anaemia, thrombocytopenia, myeloid dysplasia, Cholestasis, hepatotoxicity	Thiopurine S-methyl-transferase, Xantine oxidase
Inosine monophosphate dehydrogenase inhibitors:			
Mycofenolate mofetil **Mycofenolate**	Selective inhibition of inosine monophosphate dehydrogenase, Inhibition of B- and T-cell proliferation	Vomiting, diarrhea, abdominal pain muscle weakness, Anaemia, leucopenia	UDP-glucuronyl transferase, CYP3A4/5
Corticosteroids:			
Prednisone **Methyl-prednisolone**	Inhibition of T-cell migration and production of T-cell lymphokines	Adrenal cortex suppression Hypercholesterolemia, diabetes, hypertension, osteoporosis, osteonecrosis, cataracta, skin atrophy	CYP3A4/5

Table 1. Immunosuppressants with low molecular weight.

according to their molecular weights (agents with low or high molecular weights). High-molecular-weight agents, such as polyclonal and monoclonal antibodies (e.g., thymoglobulin, basiliximab, belatacept), that are not substrates for drug-metabolizing enzymes, are metabolized in common protein degradation pathways (intracellular catabolism by endosomal-lysosomal system) [28]; therefore, they are not subjects of metabolic drug interactions and not subjects of this review. In the metabolism of immunosuppressants with low molecular weight, drug-metabolizing CYP enzymes are involved which may entail metabolic drug interactions (**Table 1**).

3.1. Calcineurin inhibitors

For solid organ transplant recipients, the mainstay of the immunosuppressive regimens is calcineurin inhibitor (CNI) therapy with ciclosporin or tacrolimus which selectively blocks several signaling processes, resulting in the inhibition of T-cell activation and proliferation (**Figure 1**) [29, 30]. These drugs effectively treat allograft rejection; however, they display large interindividual variability in their pharmacokinetics, requiring monitoring of blood concentrations for optimal safety and therapeutic efficacy.

Ciclosporin A is an 11-amino acid cyclopeptide that blocks the production of IL-2 by inhibition of calcineurin and, as a consequence, the activation of T-cells (**Figure 1**) [31]. Ciclosporin undergoes extensive metabolism by CYP3A enzymes, producing more than 30 metabolites. The major metabolic pathways are *N*-demethylation to 4-*N*-demethyl ciclosporin, hydroxylation at several positions (1-, 6-, 9-monohydroxy and 1,9- or 6,9-dihydroxy-metabolites), and oxidation to carboxylic acid [32]. Some of the metabolites (e.g., 1,9-dihydroxy-ciclosporin,

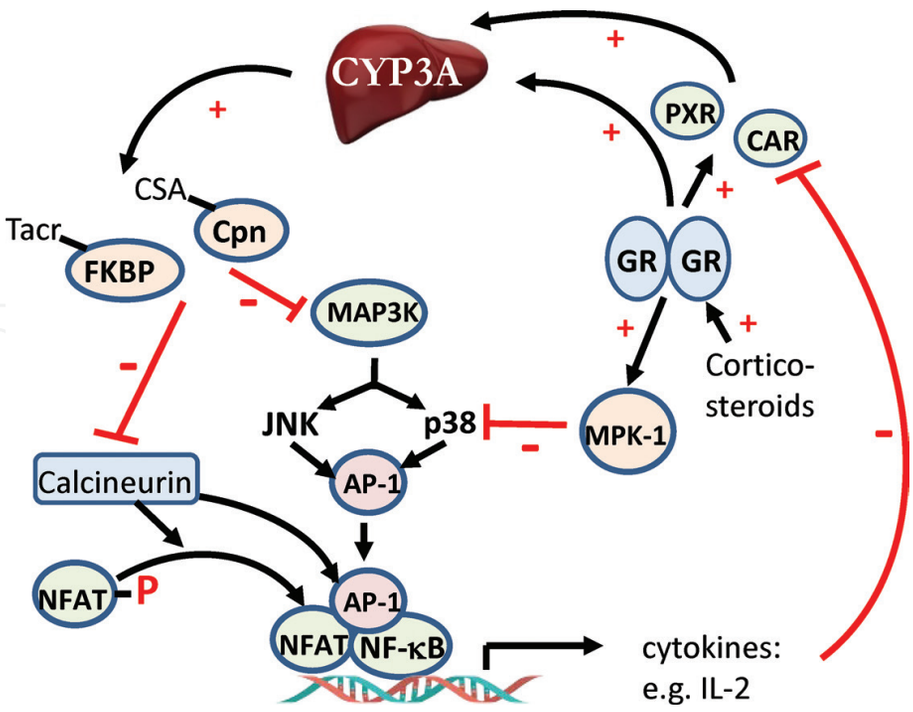

Figure 1. Molecular action of calcineurin inhibitors and corticosteriods. AP-1 activator protein 1, CAR constitutive androstane receptor, CSA ciclosporin, FKBP tarcolimus binding protein, GR glucocoticoid receptor, IL-2 interleukin 2, JNK c-Jun N-terminal kinase, MAP3K mitogen-activated protein 3 kinase, MPK-1 mitogen-activated protein kinase 1, NFAT nuclear factor of activated T-cells, PXR pregnane X receptor, Tacr tacrolimus.

1c9-dihydroxy-ciclosporin, 1-carboxy-ciclosporin) are toxic contributing to the nephrotoxic and hepatotoxic properties of the parent compound [33, 34]. Consequently, high CYP3A activity increases the rate of ciclosporin metabolism and decreases the immunosuppressive effect, which requires dose modification [35]. However, high CYP3A activity also increases the toxic metabolite formation and the risk of nephrotoxicity and hepatotoxicity. Therefore, immunosuppressive strategy must consider the blood concentrations of both ciclosporin and the toxic metabolites, especially if they are accompanied with symptoms indicating nephrotoxicity or hepatotoxicity.

Immunosuppressive properties of tacrolimus are similar to ciclosporin; however, for the same pharmacological effect, significantly lower blood concentration of tacrolimus is required than that of ciclosporin. Tacrolimus, the 23-membered macrocyclic lactone, is converted by demethylation, hydroxylation, and ring rearrangement to at least 15 metabolites, and only a minor proportion of tacrolimus dose is eliminated as unchanged parent drug [36]. Metabolism of tacrolimus leads to the inactivation of the molecule, except for the major 13-*O*-demethyl and the minor 31-*O*-demethyl metabolites. The 13-*O*-demethyl-tacrolimus possesses some immunosuppressive effect; however, it is about one tenth as active as tacrolimus, whereas the 31-*O*-demethyl metabolite displays an immunosuppressive activity comparable to tacrolimus [37, 38]. On the other hand, high blood concentration of 15-*O*-demethyl-tacrolimus metabolite has been reported to be associated with nephrotoxicity and myelotoxicity and with higher incidence of infections [39]. Similarly to ciclosporin, tacrolimus is metabolized by CYP3A enzymes, anticipating great interindividual and intraindividual differences in pharmacokinetics of tacrolimus: (1) CYP3A activity of enterocytes contributes to the first-pass metabolism of tacrolimus; (2) substantial interindividual differences in hepatic CYP3A activity result in great variability in the rate of tacrolimus metabolism, which requires continuous drug monitoring and dose modification primarily in the early postoperative period; (3) concomitant treatment with CYP3A inhibitors is the potential source of metabolic drug interactions; (4) genetic polymorphisms of CYP3A5 also contribute to the high interindividual variability. Since the relative contribution of CYP3A5 to tacrolimus biotransformation is significantly higher than that of CYP3A4 [40], the recipients carrying wild type *CYP3A5*1* allele or transplanted with liver grafts carrying *CYP3A5*1* are able to metabolize tacrolimus more rapidly than CYP3A5 nonexpressers [35, 41].

3.2. mTOR (mammalian target of rapamycin) inhibitors

The mTOR inhibitors prevent cell proliferation by blocking cell cycle progression from the G1-phase to the S-phase. The immunosuppressive activity is mediated *via* blocking mTOR protein kinases, resulting in inhibition of growth factor–mediated T-cell proliferation in response to IL-2 trigger [42]. Sirolimus is a 31-membered macrolide, whereas everolimus is a sirolimus derivative having a 2-hydroxyethyl chain substitution at position 40. Although the chemical structures of sirolimus and everolimus are similar to that of tacrolimus, the mechanism of action of mTOR inhibitors is distinct from calcineurin inhibitors, which allows the application of combination regimens. Additionally, the main advantages of mTOR inhibitors are their nonnephrotoxic properties; therefore, mTOR inhibitors in combination with reduced dose calcineurin inhibitors can augment the calcineurin inhibitor–induced nephrotoxicity [43–45].

The structural similarities can explain some common metabolic pathways of mTOR inhibitors and tacrolimus, such as *O*-dealkylation and hydroxylation at several positions [42]. Sirolimus is primarily metabolized by CYP3A enzymes and by CYP2C8 at lower extent, producing hydroxylated and *O*-demethylated metabolites (e.g., 12-hydroxy-, 16-*O*-demethyl-, 39-*O*-demethyl-, 27–39-*O*-didemethyl- and dihydroxy-sirolimus as major metabolites) [46, 47]. The metabolism of sirolimus leads to inactivation, despite the fact that some metabolites display some pharmacological activity less than one tenth of the parent drug. Everolimus is also metabolized by CYP3A and CYP2C8 enzymes; however, the elimination rate of everolimus is more rapid than sirolimus (with 30 h *vs.* 62 h elimination half-lives, respectively). Everolimus is *O*-demethylated and hydroxylated at several positions (forming both mono- and dihydroxy-metabolites); furthermore, a ring-opened metabolite is also formed from everolimus [46]. Everolimus-induced adverse effects are associated with the exposure rather to the parent compound than to its metabolites.

3.3. Antimetabolite purine analogues

One of the oldest agents with immunosuppressive activity introduced for kidney transplant recipients was the purine analogue 6-mercaptopurine, which acts by inhibiting purine nucleotide synthesis and, as a consequence, cell proliferation. The prodrug of 6-mercaptopurine, azathioprine with more favorable side-effect profile was later introduced to prevent rejection. Azathioprine is converted to 6-mercaptopurine by nonenzymatic cleavage of the thioether in enterocytes and hepatocytes or in erythrocytes. The major active metabolites, 6-thioguanine nucleotides, are formed *via* 6-thioinosine monophosphate in natural purine synthetic pathways. Inhibition of cell proliferation is mediated by incorporation of the thiopurine nucleotide analogues into DNA (and RNA), causing DNA damage [48]. 6-Mercaptopurine, independently from either direct administration or production from azathioprine, undergoes metabolic inactivation by xanthine oxidase and thiopurine S-methyl transferase and is excreted in the urine, leaving less parent compound available to form thiopurine nucleotides [49]. Due to genetic polymorphism, the thiopurine S-methyl transferase activity is highly variable in patients; namely, those subjects who carry one or two nonfunctional thiopurine S-methyl transferase alleles are unable to tolerate normal doses of azathioprine and can experience serious myelosuppression [50]. Therefore, genotyping assay is recommended before starting azathioprine therapy to identify high-risk patients, and dosage reduction or alternative therapy is recommended for these patients.

3.4. Inosine monophosphate dehydrogenase inhibitors

Mycophenolic acid is a selective inhibitor of inosine monophosphate dehydrogenase, which is responsible for *de novo* biosynthesis of guanosine monophosphate, one of the building blocks of DNA. Depletion of the guanosine pool in the cell arrests the lymphotic cell proliferation and suppresses the subsequent immune response triggered by allogenic transplanted organ [51]. In several rapidly dividing cells (e.g. enterocytes), an alternative salvage pathway exists for purine synthesis in addition to *de novo* synthetic pathway; however, lymphocytes seem to be dependent on the *de novo* pathway. Consequently, mycophenolic acid is able to selectively block proliferation of T- and B-cells. Mycophenolic acid is available as enteric-coated mycophenolate sodium and as mycophenolate mofetil ester prodrug that is extensively hydrolyzed to the active metabolite mycophenolic acid by carboxylesterases.

Mycophenolic acid is primarily metabolized by UDP-glucuronyl transferases (UGT1A7/8/9, UGT2B7), forming the major 7-*O*-mycophenolic glucuronide that is pharmacologically inactive and to the minor acil-glucuronide that has pharmacological activity comparable to the mycophenolic acid [52, 53]. The major proportion of the glucuronide conjugates is excreted in urine, whereas a smaller proportion that is eliminated *via* bile is metabolized by bacteria in the gut, and the deconjugated mycophenolic acid can be reabsorbed (enterohepatic circulation) [54]. Furthermore, in patients' blood and urine, a minor demethylated metabolite (6-*O*-demethylmycophenolic acid) was also detected that was proved to be produced by CYP3A enzymes.

3.5. Corticosteroids

At the beginning of transplantation history, glucocorticosteroids were the primary immunosuppressive agents in the rejection prophylaxis strategy, and nowadays, they are still the first-line agents for treatment of graft rejection. The high-dose glucocorticoids given in peritransplantation are tapered to low doses in the maintenance phase, aiming the steroid-free immunosuppression regimens because of serious adverse effects of glucocorticoids developing in long-term therapy. Acute rejection is generally treated with methylprednisolone, whereas the maintenance therapy applies either methylprednisolone or prednisone. Corticosteroids activate the cytosolic glucucorticoid receptor and modulate several cellular functions, including transcription of genes involved in proliferative and inflammatory processes. The activated receptor inhibits the transcription of NF-kB and activator protein 1 dependent genes, including proinflammatory cytokines (**Figure 1**). This process leads to the depletion of T-cells and macrophage dysfunction [55].

Regioselective and stereospecific hydroxylation of corticosteroids at several positions (at carbon 2, 6, 7, 15, 16, and 21) are catalyzed by CYP3A enzymes. Additionally, dual effect of corticosteroids on CYP3A enzymes has been demonstrated: (1) corticosteroids can competitively inhibit the function of CYP3A [56], and (2) they can induce CYP3A transcription. Activated glucocorticoid receptor upregulates the expression of nuclear receptors (PXR and CAR) that are involved in transcriptional regulation of CYP3A genes. Moreover, the proximal promoter region of CYP3A4 gene contains glucocorticoid responsive element, which directly binds activated glucocorticoid receptor [18, 57]. As a consequence of increased expression and activity of CYP3A enzymes, metabolic drug interactions can be expected upon concomitant treatment with drugs that require CYP3A activity for their metabolism.

3.6. Novel investigational immunosuppressant agents

Although calcineurin inhibitor–based immunosuppression efficiently prevents rejection, adverse reactions of ciclosporin and tacrolimus, primarily nephrotoxicity, prompt the discovery of novel agents with immunosuppressive activity [58]. Two investigational agents with low molecular weight should be mentioned: voclosporin and sotrastaurin. Voclosporin, a next-generation calcineurin inhibitor, is an analogue of ciclosporin with a single carbon extension added to the amino acid-1 of ciclosporin. Voclosporin displays higher binding affinity to cyclophillin A than ciclosporin leading to more potent inhibition of calcineurin [59]. Furthermore, it has a favorable safety property that it appears to be less toxic than currently available calcineurin

inhibitors. Similarly to ciclosporin, voclospiron is a substrate for CYP3A enzymes, anticipating pharmacokinetic/metabolic drug interactions with those agents that interact with ciclosporin as well [60]. However, voclosporin is no longer pursed in transplantation. Sotrastaurin is protein kinase C inhibitor that effectively inhibits IL-2 production with the mechanism different from calcineurin or mTOR inhibition. Although sotrastaurin displayed some potential in preventing allograft rejection in animal studies, high efficacy and safety failure rate were observed in clinical trials involving kidney and liver transplant patients [61, 62]. Therefore, further development of sotrastaurin in transplantation has been halted.

4. Significant metabolic drug interactions with immunosuppressants

4.1. Combined immunosuppressive therapy

Transplant recipients' immunosuppressive therapy is often a multidrug therapy, primarily in the early postoperative period, which constitutes a challenge for clinicians to consider the complexity of drug interactions. Due to the fact that the metabolism of immunosuppressants with low molecular weight is catalyzed by the same enzymes (CYP3A4 and CYP3A5), the blood concentrations, elimination half-lives, and consequently, the efficacy or toxicity of certain immunosuppressant agents are expected to be modified during concomitant treatment. Therefore, during multidrug therapy or during withdrawal of any of the immunosuppressive drugs, special attention is required for optimal dosing for therapeutic concentrations. Each modification in immunosuppressive regimens can lead to changes in blood concentration of a drug (**Table 2**).

Calcineurin inhibitors are often applied in combination with mTOR inhibitors. Since both mTOR inhibitors and calcineurin inhibitors are substrates of CYP3A enzymes and can inhibit CYP3A activities, reduction of calcineurin inhibitor doses is recommended. Standard doses of ciclosporin were observed to decrease the clearance of sirolimus or everolimus more substantially than the doses of tacrolimus [45]. The major drawback of calcineurin inhibitor therapy is the risk of nephrotoxicity which appears to be dose dependent. The combination of low calcineurin inhibitor doses with mTOR inhibitors was found to be beneficial regarding retaining low rejection rates and lowering the risk of nephrotoxicity [44, 63]. To avoided renal dysfunction, the complete substitution of calcineurin inhibitors for mTOR inhibitors was attempted; however, the substitution showed an increase in graft failure in patients treated with merely mTOR inhibitors [64].

Corticosteroids have been demonstrated to induce the expression of the efflux pump transporter ABCB1 (P-glycoprotein) playing a main role in intestinal drug absorption and of CYP3A enzymes responsible for the metabolism of the majority of drugs [18, 65]. Therefore, the concomitant treatment of calcineurin inhibitors or mTOR inhibitors with corticosteroids can be expected to decrease the blood concentrations of tacrolimus/ciclosporin or of sirolimus/everolimus. Although the evidence for clinically significant interactions between corticosteroids and ciclosporin or mTOR inhibitors is limited, clear clinical effect of corticosteroids on tacrolimus exposure has been demonstrated [66, 67]. This also implies that dose reduction or cessation of corticosteroids leads to an increase in blood concentrations of tacrolimus, requiring dose

Immunosuppressant	Drug interactions	Consequences
Ciclosporin Tacrolimus	sirolimus, everolimus	Increased blood levels of ciclosporin and mTOR inhibitors; increased risk of nephrotoxicity
	prednisolone	Decreased blood levels due to enhanced metabolism of ciclosporin/tacrolimus, increased risk of rejection
	Antifungals:	
	ketoconazole	Increased blood levels of ciclosporin/tacrolimus; replacement of ketoconazole to other azole derivatives
	fluconazole, voriconazole, itraconazole	Inhibition of CYP3A4; dose reduction of ciclosporin, tacrolimus is necessary
	Antibiotics:	
	clarithromycin, erythromycin, azithromycin	Irreversible inhibition of CYP3A4; increased blood levels of ciclosporin/tacrolimus
	rifampicin	CYP3A4 induction; enhanced metabolism of ciclosporin, tacrolimus; increased risk of rejection
	Antiviral agents:	
	ritonavir	Irreversible inhibition of CYP3A4; increased blood levels of ciclosporin/tacrolimus
	Lipid-lowering agents:	
	fluvastatin, simvastatin, atorvastatin	Increased statin exposure by ciclosporin; incrased risk of myopathy and rhabdomyolysis
	Antihypertensive agents:	
	diltiazem, verapamil, amlodipine	Irreversible inhibition of CYP3A4, formation of metabolic intermediate complex; Increased blood levels of ciclosporin / tacrolimus
	nifedipine	Reversible, competitive inhibition CYP3A4
	carvedilol	Inhibition of ABCB1 transporter; increase absorption of oral ciclosporin
	Antidiabetic agents:	
	troglitazone, rosiglitazone	CYP3A4 induction; enhanced metabolism of ciclosporin/tacrolimus; increased risk of rejection
	Psychopharmacons:	
	carbamazepine, valproic acid	CYP3A4 induction; enhanced metabolism of ciclosporin/tacrolimus; increased risk of rejection
	fluvoxamine	Inhibition of CYP3A4; contraindicated
	Herbs:	
	St John's wort	CYP3A4 induction; enhanced metabolism of ciclosporin/tacrolimus; increased risk of rejection
	grapefruit, pomelo	Irreversible inhibition of CYP3A4; increased blood levels of ciclosporin/tacrolimus

Immunosuppressant	Drug interactions	Consequences
Sirolimus Everolimus	ciclosporin	Increased blood levels of ciclosporin and mTOR inhibitors; increased risk of nephrotoxicity
	prednisolone	Decreased blood levels due to enhanced metabolism of sirolimus/everolimus, increased risk of rejection
	Antifungals:	
	ketoconazole	Increased blood levels of mTOR inhibitors; replacement of ketoconazole to other azole derivatives
	fluconazole, voriconazole, itraconazole	Inhibition of CYP3A4; dose reduction of sirolimus, everolimus is necessary; voriconazole – sirolimus combination is contraindicated
	Antibiotics:	
	clarithromycin, erythromycin, azithromycin	Irreversible inhibition of CYP3A4; increased blood levels of sirolimus/everolimus
	rifampicin	CYP3A4 induction; enhanced metabolism of sirolimus/everolimus; increased risk of rejection
	Antiviral agents:	
	ritonavir	Irreversible inhibition of CYP3A4; increased blood levels of sirolimus/everolimus
	Antihypertensive agents:	
	diltiazem, verapamil, amlodipine	Irreversible inhibition of CYP3A4, formation of metabolic intermediate complex; Increased blood levels of sirolimus/everolimus; verapamil-sirolimus combination is associated with increased blood levels of verapamil
	Antidiabetic agents:	
	troglitazone, rosiglitazone	CYP3A4 induction; enhanced metabolism of sirolimus/everolimus; increased risk of rejection
	Psychopharmacons:	
	carbamazepine, valproic acid	CYP3A4 induction; enhanced metabolism of sirolimus/everolimus; increased risk of rejection
	Herbs:	
	St John's wort	CYP3A4 induction; enhanced metabolism of sirolimus/everolimus; increased risk of rejection
	grapefruit, pomelo	Irreversible inhibition of CYP3A4; increased blood levels of sirolimus/everolimus
6-mercaptopurine Azathioprine	allopurinol	Inhibition of xantine oxidase; myelotoxicity
Mycophenolate	Ciclosporin	Inhibition of enterohepatic circulation, decrease in blood levels of mycophenolic acid

Immunosuppressant	Drug interactions	Consequences
	Antiviral agents:	
	ganciclovir, valganciclovir	Mycophenolate-glucuronide inhibits renal tubular secretion of ganciclovir; increased blood levels of ganciclovir and increased risk of toxicity (nephrotoxicity, neutropenia, leukopenia)
Prednisolone Methylprednisolone	*Antifungals*:	
	ketoconazole, fluconazole, voriconazole, itraconazole	Increased blood levels of corticosteroids Inhibition of CYP3A4
	Antibiotics:	
	rifampicin	CYP3A4 induction; enhanced metabolism of corticosteroids
	Antiviral agents:	
	ritonavir	Irreversible inhibition of CYP3A4; increased blood levels of corticosteroids

Table 2. Clinically relevant pharmacokinetic drug interactions with immunosuppressants.

adjustment [68]. Interestingly, CYP3A5 nonexpressers with *CYP3A5*3/*3* genotype are more susceptible to glucocorticoid induction than *CYP3A5*1* carriers [69]; thus, more pronounced increase in tacrolimus exposure can be expected in CYP3A5 nonexpressers after glucocorticoid withdrawal.

Clinically significant interaction between mycophenolic acid, the active metabolite of mycophenolate mofetil, and ciclosporin has been reported [70]. The mycophenolate-glucuronide metabolite eliminated into bile undergoes enterohepatic cycling because of intestinal bacterial metabolism and reabsorption of mycophenolic acid. The enterohepatic circulation, contributing to overall pharmacokinetics of mycophenolic acid by 37% in human, is inhibited by concomitant administration of ciclosporin but does not interfere with tacrolimus or sirolimus [71, 72]. In ciclosporin-mycophenolate combination therapy, the reduced blood concentration of mycophenolic acid is necessary to ameliorate by increasing dose of mycophenolate mofetil. Furthermore, special attention on optimal dosing is required during switching ciclosporin-mycophenolate to tacrolimus-mycophenolate therapy and *vice versa*.

4.2. Metabolic drug interactions between immunosuppressants and post-transplant medication

4.2.1. Treatment and prevention of infections

Environmental circumstances and immune deficiencies due to immunosuppression therapy make recipients susceptible for infections that are one of the leading complications after organ transplantation; therefore, prevention and management of infections is a major task

primarily in the early postoperative period. Since fungal infections are a threatening cause of morbidity and mortality, the antifungal prophylaxis is an important element of posttransplant medication. The antifungal azole-derivatives are potent (some of them are very strong) CYP3A inhibitors, predicting potential metabolic drug interactions with calcineurin inhibitors, mTOR inhibitors, or corticosteroids. The most potent CYP3A inhibitor is ketoconazole, able to increase blood concentrations (AUC) of ciclosporin (> 4-fold), tacrolimus (> 2-fold), sirolimus (11-fold), everolimus (15-fold), and methylprednisolone (> 2-fold) [73, 74]. Because of the substantial increase in blood concentrations of several immunosuppressants that can be avoided by drastic reduction of immunosuppressant doses and because of other adverse effects of ketoconazole, the concomitant medication is discouraged. Fluconazole, itraconazole, and voriconazole are alternative regimens for antifungal therapy or prophylaxis; however, all three drugs are azole derivatives and have the capability to inhibit CYP3A function, albeit at a lower extent than ketoconazole [75–77]. Although the continuous immunosuppressant monitoring is highly recommended and dose adjustment (reduction) is generally required, the antifungal treatment with fluconazole, itraconazole, or voriconazole can be safely applied except for voriconazole-sirolimus combination [78]. Because of an extreme (7-fold) increase of sirolimus blood concentrations as a consequence of concomitant use of voriconazole, this combination is contraindicated. Amphotericin B, the nonazole type antifungal agent, does not influence CYP activities; therefore, no metabolic drug interactions can be expected in concomitant treatment with immunosuppressants. However, the widespread use of amphotericin B is limited because of its toxicity profile, primarily because its nephrotoxic side-effect can contribute to the renal injury by ciclosporin or tacrolimus.

Organ transplant patients are at high risk for developing bacterial infections that occur in 20–40% of transplants. Potential sources of infection are from hospital and community exposures, as well as from endogenous flora of patients. Among the antibiotics used for treatment of infections, the macrolide erythromycin and clarithromycin have been reported to interact with immunosuppressive agents. These macrolides are CYP3A substrates and bind to CYP3A4 enzymes, leading to a complex formation that completely inactivates CYP3A4 enzyme [79–82]. The *in vitro* findings were confirmed by clinical observations that blood concentrations of ciclosporin/tacrolimus or sirolimus/everolimus increased as a consequences of concomitant treatment with erythromycin or clarithromycin [73, 83–86]. Page et al. [87] and Mori et al. [88] have reported some potential of azithromycin for drug interaction with ciclosporin and tacrolimus; however, *in vitro* experiments demonstrated that azithromycin poorly interfere with CYP3A4 [89]. When concomitant therapy with these macrolides is necessary, blood concentrations of calcineurin inhibitors or mTOR inhibitors should be carefully monitored, and the immunosuppressant doses should be adjusted. In contrast, the macrolide rifampicin is a potent CYP3A4 inducer and can activate PXR, resulting in a substantial increase in CYP3A4 expression [90]. The increased CYP3A4 activity consequently enhances the metabolism and elimination of calcineurin inhibitors, mTOR inhibitors, and corticosteroids [91–93]. However, blood concentration–guided dose-adjustment of immunosuppressants should be applied carefully because increased metabolism can evoke elevation of toxic metabolite formation (e.g., ciclosporin).

A significant cause of graft failure still remains viral infections, which are acquired as new infection or reactivation of latent viruses. After transplantation, cytomegalovirus (CMV) is the

most common viral infection in recipients, primarily in those CMV-seronegative patients who were transplanted with graft from CMV-seropositive donors, resulting in viral reactivation. For prophylaxis and treatment of CMV infection, aciclovir, ganciclovir, and valganciclovir (the prodrug of ganciclovir) are generally applied. None of these antiviral drugs influences the function of drug-metabolizing CYPs or UDP-glucuronyl transferases, and consequently, they do not modify the pharmacokinetic properties of immunosuppressants. Aciclovir and ganciclovir are eliminated primarily in the urine as unchanged compounds. Increased risk of nephrotoxicity and leukopenia has been reported in patients who were co-medicated with a drug that can reduce renal clearance of aciclovir or ganciclovir. During co-administration with mycophenolate or mycophenolate-mofetil, mycophenolate-glucuronide and aciclovir or ganciclovir can significantly compete for renal tubular secretion, resulting in an increase in aciclovir/ganciclovir and mycophenolate-glucuronide exposure, as well as the risk of nephrotoxicity or leukopenia [94–96]. Management of potent metabolic drug interactions between antiviral protease inhibitors and immunosuppressants is a major challenge because most of the protease inhibitors are clinically significant CYP3A4 inhibitors. Ritonavir-boosted therapies require substantial reduction of immunosuppressant doses (to 5–20% for ciclosporin; to 1–3.5% for tacrolimus) with continuous monitoring of blood concentrations [97–101].

4.2.2. Treatment of dyslipidemia

Dyslipidemia is often developed as an adverse impact of immunosuppressive therapy [102]. Ciclosporin, mTOR inhibitors, and prednisone are mainly implicated in lipid alterations. For treatment of hypercholesterolemia, the basic guidelines for dyslipidemia recommend diet and HMG-CoA reductase (hydroxymethyl-glutaryl-CoA reductase) inhibitor statins with special considerations for transplant patients. Although both ciclosporin and most statins (atorvastatin, fluvastatin, simvastatin, lovastatin) are primarily metabolized by CYP3A4 and metabolic drug interactions are likely occur, statins do not evoke increased ciclosporin exposure [103–106]. In contrast, ciclosporin induces significant elevation of statin blood concentrations which can be explained by the ten-fold higher molar concentrations of ciclosporin than statins. In combination with ciclosporin, the blood levels are increased in a statin-dependent manner, e.g., lovastatin is increased to a much greater extent than atorvastatin [104, 107]. Dose reduction of lipid-lowering agents is recommended to avoid myopathy or rhabdomyolysis. The blood concentrations of macrolide immunosuppressants (tacrolimus, sirolimus, and everolimus) are similar to that of statins [108, 109]; therefore, the lack of clinically relevant interactions between macrolides and statins is not unexpected.

4.2.3. Antihypertensive agents

Organ transplantation and immunosuppressive therapy (e.g., ciclosporin, prednisone) frequently trigger hypertension or worsen the preexisting disease in patients. While most of the antihypertensive agents (β-adrenoceptor blockers, α1-adrenergic receptor antagonists, central α2-adrenergic receptor agonists, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers) are not expected to influence the pharmacokinetics of immunosuppressants, medication with diltiazem, verapamil, or amlodipine requires special consideration and

frequent monitoring of immunosuppressant blood concentrations. The metabolism of all three Ca-channel blockers is primarily catalyzed by CYP3A4, anticipating potential drug interactions with immunosuppressants. Furthermore, significant inhibition of CYP3A4 by diltiazem, verapamil, and amlodipine has been demonstrated with an additional inhibitory property of metabolite intermediate complex formation that catalytically inactivates CYP3A4 and CYP3A5 enzymes [79, 80, 82, 110–114]. The inactivation of CYP3A enzymes by comedication with these antihypertensive drugs consequently leads to a permanent increase in blood concentrations of calcineurin inhibitors or mTOR inhibitors [115–122]. In transplant recipients comedicated with sirolimus and verapamil, an increase of blood concentrations of both sirolimus and verapamil was observed [123]. Furthermore, in patients carrying wild-type *CYP3A5*1* allele, concomitant treatment with amlodipine significantly decreased tacrolimus clearance, and along with the changes in tacrolimus pharmacokinetics, an increase in amlodipine blood concentrations was also observed [124]. The metabolism of the Ca-channel blocker nifedipine is catalyzed almost exclusively by CYP3A enzymes, and competition for the active site of CYP3As may be expected if nifedipine and CYP3A substrate calcineurine inhibitors or mTOR inhibitors are concomitantly applied. In contrast, no evidence for pharmacokinetic drug interactions has been provided in transplant recipients treated with nifedipine and ciclosporin/tacrolimus or sirolimus/everolimus. Carvedilol is often used for treatment of hypertension in transplant patients, and pharmacokinetic drug interaction between carvedilol and ciclosporin has been observed that required 10–20% reduction of ciclosporin doses to maintain the blood concentrations within the therapeutic range [125, 126]. The major metabolic pathways of carvedilol are catalyzed by CYP2D6 and CYP1A2 rather than by CYP3A4 [127]; however, inhibition of CYP3A enzymes by carvedilol does not account for pharmacokinetic drug interaction with ciclosporin. Carvedilol has been demonstrated to block the function of the ABCB1 transporter protein (ATP-binding cassette B1; previously called as Pgp) [128]. In the intestinal wall, ABCB1 transporter pumps pharmacons or other xenobiotics passed into the enterocytes back into the gut lumen. The inhibition of ABCB1-mediated transcellular transport in the intestine by carvedilol is responsible for the increased absorption of ciclosporin. Under careful monitoring of ciclosporin blood concentration, the ABCB1 inhibition by carvedilol can be beneficial in ciclosporin-sparing therapy for transplant patients. Since the absorption of tacrolimus and mTOR inhibitors is also mediated by ABCB1, similar pharmacokinetic drug interactions between these immunosuppressants and carvedilol are presumably developed as with ciclosporin.

4.2.4. Antihyperglycemic therapy

Hyperglycemia developing posttransplant diabetes mellitus is generally medication related. Corticosteroids can evoke reduction of glucose tolerance, whereas ciclosporin and tacrolimus directly block insulin-release by islet cells. The metabolism of the sulfonylurea type antidiabetic agents (e.g., tolbutamide, glipizide, glibenclamide, and glimepiride) is mediated by CYP2C9; therefore, metabolic drug interactions with immunosuppressants are not expected in patients treated with any of these oral hypoglycemic drugs. Although the thiazolidinedione type troglitazone and rosiglitazone are not CYP3A substrates, they can induce the expression of CYP3A enzymes by activation of the nuclear receptors, PXR and CAR [129–132]. Enhanced transcription results in an increase in CYP3A activities and the metabolism of calcineurin inhibitors,

mTOR inhibitors and corticosteroids, increasing the risk of rejection [133]. Immunosuppressant dose adjustment is required to avoid subtherapeutic blood concentrations, and careful monitoring of immunosuppressant blood concentrations is recommended during withdrawal of troglitazone or rosiglitazone and during switching to other antihyperglycemic agent.

4.2.5. Psychiatric medication

The most common psychiatric disorders encountered in transplant patients are anxiety, depression, mood disorders, behavior problems, and insomnia that are reversible in most cases; however, they often require psychotherapy with antidepressants, mood stabilizers, anxiolytic agents, or even with antipsychotics. Many of these pharmacons are metabolized by enzymes other than CYP3A4 and do not influence the drug-metabolizing activities of CYP3A4; consequently, metabolic drug interactions with immunosuppressants cannot be expected. Nevertheless, the CYP3A4 inducing or inhibitory properties of some of these psychopharmacons should be considered. The mood stabilizer carbamazepine and valproic acid have been clearly evidenced to be able to activate CAR and PXR. The nuclear receptor activation leads to an increase in transcription of *CYP3A4* gene and CYP3A4 metabolic activity [134, 135], anticipating decrease of immunosuppressant blood concentrations [136]. To reduce the risk of organ rejection, adjustment (increase) of immunosuppressant doses is required with continuous monitoring of immunosuppressant blood levels. Furthermore, the CYP3A4 deinduction process can last for about 2 weeks after cessation of carbamazepine or valproic acid [137]; thus, careful monitoring of immunosuppressant blood concentrations during withdrawal is essential. The comedication with the antidepressant fluvoxamine is contraindicated because of its strong inhibitory properties for CYP3A4 substrates and potential drug interactions with ciclosporin/tacrolimus or with sirolimus/everolimus [80, 138, 139]. For psychotherapeutic agents that are CYP3A substrates (haloperidol, quetiapine, clonazepam, midazolam, alprazolam), continuous monitoring of immunosuppressant blood levels is highly recommended to avoid metabolic drug interactions.

4.2.6. Treatment of hyperuricemia

The metabolic drug interactions with ciclosporin/tacrolimus, sirolimus/everolimus, and corticosteroids are generally associated with reversible or irreversible inhibition of CYP3A activities, as well as with transcriptional induction of CYP3A4 and CYP3A5 expression. Clinically significant drug interaction occurs during simultaneous therapy with azathioprine (or 6-mercaptopurine) and allopurinol, the antihyperuricemic agent [140, 141]; however, it involves enzyme other than CYP3As. The metabolism of both 6-mercaptopurine and allopurinol is catalyzed by xantine oxidase, anticipating metabolic drug interactions and developing serious adverse reactions. As a consequence of inhibition of xantine oxidase by allopurinol, myelotoxicity is evoked by the accumulation of 6-thioguanine-nucleotide metabolites of azathioprine. The risk of bone marrow depletion is increased in patients with low thiopurine methyl-transferase activity. To avoid the serious myelosuppression during treatment of hyperuricemia and gout, substantial reduction of azathioprine dose (by at least 50%) is required when allopurinol is given concomitantly, or alternative agents other than allopurinol should be considered [142–144].

4.3. Metabolic drug interactions between immunosuppressants and herb components

Pharmacokinetic herb-drug interactions can also significantly influence the outcome of immunosuppressive therapy and long-term graft survival [145]. St John's wort (*Hypericum perforatum*) extract and grapefruit juice are well described as modifiers of pharmacokinetic properties of ciclosporin and tacrolimus [146–148]. St John's wort extract is a herbal product for treatment of symptoms of mild or moderate depression, including anxiety, fatigue, and sleeping problems. The extract contains a number of biologically active components, e.g., hyperforin of high interest. Hyperforin has a strong affinity for PXR and significantly increases the expression and activities of CYP3A4 enzyme, which is involved in metabolism of many drugs [149, 150]. Consequently, chronic consumption of St John's wort extract can decrease the blood concentrations of CYP3A substrates, such as calcineurin inhibitors, mTOR inhibitors, and corticosteroids [151–154]. In addition, St John's wort extract has been reported to induce the expression of ABCB1 transporter that reduces the absorption of ABCB1-ligand drugs from the gut. The hyperforin contents of commercially available St John's wort preparations are variables that appear to significantly affect the extent of pharmacokinetic interactions [150, 155]. Coadministration of ciclosporin with St John's wort extract has been reported to lead a 40–60% decrease of ciclosporin blood concentrations, increasing the risk of rejection; therefore, substantial dose adjustment is required [151, 152, 155–159]. Since clinicians are often unaware of concomitant consumption of herbal supplements, transplant patients should be informed about the drug interaction potential of St John's wort that can endanger the success of organ transplantation.

Concomitant intake of grapefruit (*Citrus paradisii*) or pomelo (*Citrus grandis*) has been demonstrated to increase the bioavailability of immunosuppressants [147, 160, 161]. Some components of these citrus fruits, bergamottin and naringenin responsible for the bitter taste, can inhibit the activities of CYP3A4 and CYP3A5 enzymes both in the intestinal wall and in the liver, resulting in significant reduction of first-pass metabolism of CYP3A substrates, including ciclosporin and tacrolimus [162–164]. Significant reduction of ciclosporin/tacrolimus doses is necessary to avoid the risk of nephrotoxicity or other adverse events associated with immunosuppressive therapy. The furanocoumarin bergamottin is a "suicide substrate," namely it is metabolized by CYP3A4 to an epoxid metabolite that covalently binds to and inactivates the enzyme [165]. The flavonoid naringenin was found to be a less-potent CYP3A4 inhibitor than bergamottin [166]; however, during consumption of grapefruit, the inhibitory effects of naringenin and bergamottin are added together. Since clear evidence of bergamottin content and CYP3A4 inhibitory potential of citruses other than grapefruit and pomelo was provided [167], the transplantation centers do not recommend citrus consumption for transplant patients during immunosuppressive therapy.

5. Concluding remarks

Although success of organ transplantation is continuously improving, several short- and long-term complications can adversely affect the outcome. One of the most significant factors influencing the long-term graft and patient survival is the appropriate immunosuppressive

therapy. Subtherapeutic blood concentrations of immunosuppressive drugs can evoke acute or chronic graft injury mediated by immunological mechanisms, whereas overdosing leads to over-suppression of the immune system that consequently develops serious infections, as well as adverse and even life-threatening side effects. Because of the narrow therapeutic indexes, dosing of most of the immunosuppressive agents is applied under careful monitoring of their blood concentrations. The knowledge of the potential factors that can modify immunosuppressive therapy, as well as pharmacokinetic and metabolic drug interactions, can decrease the fluctuation of immunosuppressant blood concentrations, can facilitate to avoid the serious adverse events, can improve the therapeutic outcome for transplant patients, and can reduce the medical costs.

The appropriate and tailored immunosuppressive medication is a great challenge and requires careful and continuous attention, because unrecognized simple interactions can induce serious complications. As such during administratrion of clarithromycin or antifungal agents without dose reduction of calcineurin inhibitors or mTOR inhibitors, blood concentrations of immunosuppressants can substantially exceed the therapeutic range within some days. Without dose modification, a reverse outcome is expected during comedication with anticonvulsants (valproic acid and carbamazepine) or with rifampicin resulting in subtherapeutic blood concentrations of immunosuppressants and increasing the risk of organ rejection. The lack of mycophenolate dose reduction during cessation of ciclosporin or replacement of ciclosporin to another immunosuppressant can also evolve development of serious adverse reactions. It is anticipated that the special attention and the knowledge of potential drug interactions can prevent the majority of misdosing-induced adverse events.

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Conflict of interest

The author declares that there is no conflict of interest.

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