REVIEW ARTICLE

Drug Interactions between Antimicrobial and Immunosuppressive Agents in Solid Organ Transplant Recipients

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Abstract

The number of allogeneic solid organ and bone marrow transplants is increasing all over the world. To prevent transplant rejection and treat acute rejection of transplant, immunosuppressant drugs are used. The outcomes of solid organ transplants have dramatically improved over last 30 years, due to availability of multiple immunosuppressive agents, with varied mechanisms of action. The use of intense immunosuppression makes the individual having undergone solid organ transplant at the risk of several serious infections, which may prove fatal. To prevent and treat these infections (when they occur), patients are often given antimicrobial prophylaxis and therapy. The use of antimicrobials can interfere with the metabolism of the immunosuppressants, and may put the patient at risk of developing severe adverse effects due to unwanted increase or decrease in the serum levels of immunosuppressive agents. Knowledge of these interactions is essential for successful management of solid organ transplant patients. We therefore decided to review the literature and present the interactions that commonly occur between these two life-saving groups of drugs.

Keywords: Antimicrobials, Calcineurin inhibitors, Corticosteroids, Drug–drug interaction, Immunosuppressants, Intravenous immunoglobulin, Monoclonal antibodies, mTOR inhibitors, Solid organ transplant.

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Introduction

Immunosuppression plays a vital role in the success of solid organ transplant by preventing graft rejection, thus improving graft survival. The graft survival rate has increased significantly over the last 50 years with the advances in immunosuppressive therapy. Steroids and azathioprine were the only immunosuppressants available in early 1980s, with <50% graft survival rates at 1 year. With the introduction of cyclosporine, the survival rate increased to >80%. Currently, with the newer immunosuppressant drugs such as mycophenolate mofetil (MMF), tacrolimus, and anti-thymocyte globulin (ATG), graft survival has improved to >90%.[1] The commonest adverse effect of immunosuppression is increased number of infections and less commonly drug toxicity and malignancy. To obtain optimum immunosuppression and avoid undesirable adverse effects, a combination of multiple immunosuppressants with different mechanism of actions is used (combination allowing lower doses than usual). The three stages of immunosuppression are induction, maintenance, and treatment of rejection. During the maintenance phase, commonly the "triple drug regimen" (tacrolimus, MMF, and prednisone or some other combination) is used.[2]

The most common complication of immunosuppression in solid organ transplant (SOT) is infections with a large number of bacteria, fungi, viruses, and parasites. Immunosuppressants are given in high doses in initial posttransplant period to prevent acute rejection. The recipient is more susceptible to get infections during this period and hence antimicrobial prophylaxis is given. While diagnosing and treating the infectious complications of immunosuppression, the clinician must consider the following:

- The risk of infection is higher in the first few months after transplant but it may increase anytime when the patient's cumulative immunosuppression increases, e.g., during the treatment of a rejection episode.[3]
- Due to decreased innate and adaptive immune response, the classical signs and symptoms of infections are not usually seen, making it difficult to diagnose an infectious disease. A high index of suspicion is warranted.
- Noninfectious complications can mimic infection, e.g., graft-vs-host-disease (GVHD) flare, transplant rejection, and drug toxicity (e.g., sirolimus-induced pneumonitis).[4]
- One of the most important concerns while treating infectious diseases in SOT is significant interactions between

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immunosuppressants and antimicrobials.[5] Appropriate dosing and delivery of antimicrobials in immunosuppressed patients with organ dysfunctions is a major therapeutic challenge.

Depending on the time after the solid organ transplantation, the nature of infections and microbes causing the infections changes.[6] Depending on the timeline, patients are given antimicrobial prophylaxis; these drugs will then have interactions with the immunosuppressants the patient may be receiving as per duration after the solid organ transplant.[5]

Drug Interactions between Antimicrobials and Immunosuppressants

Drug–drug interactions can be classified in various ways: pharmaceutical interactions; pharmacokinetic interactions, which involve absorption, distribution (with protein and tissue binding, tissue binding), hepatic or nonhepatic metabolism, and renal or nonrenal excretion; and finally direct and indirect pharmacodynamic interactions.[7] However, for the purpose of this review we will consider the two main types, i.e., pharmacodynamic and pharmacokinetic interactions between antimicrobials and immunosuppressants.

Pharmacodynamic Interactions

This refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action.[8] So the drugs may increase or decrease each other's efficacy or toxicity, thus it can be beneficial or harmful, both. Several examples of pharmacodynamic interactions among medications used in transplant recipients have been identified. For example, an increase in renal toxicity is observed with the coadministration of naproxen and cyclosporine A. Administration of tacrolimus with antimicrobials having nephrotoxicity increases the incidence and severity of renal damage.[9]

Pharmacokinetic Interactions

Pharmacokinetics deals with the handling of the drug by the body and can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Pharmacokinetic interactions are defined as drug–drug interactions that alter the plasma concentration of one or both drugs. These interactions affect drug metabolism and disposition at each of the stages described above. There are several mechanisms by which drug interactions can occur. Many interactions occur secondary to effects on drug-metabolizing enzymes or drug transporters. Drug-metabolizing enzymes are known to alter drug absorption and metabolism. Drug transporters are likely to affect drug absorption, distribution, and elimination. The following enzymes metabolize most frequently used immunosuppressants (Table 1).

CYP3A Modulation

Immunosuppressive drug interactions can be caused by an anti-infective agent directly inhibiting cytochrome P450 3A4 (here abbreviated to CYP3A4) or via drug competition for CYP3A4 substrate sites. Both mechanisms may result in increased immunosuppressive concentrations. In contrast, CYP3A4 induction via increased synthesis or decreased breakdown of CYP isoenzymes may result in decreased concentrations of immunosuppressants (Table 2).[9,10]

Phenytoin is a known inducer of CYP3A and CsA is a substrate of CYP3A. The ligand (phenytoin) binds to the pregnane X receptor (PXR) [also called steroid and xenobiotic-sensing nuclear receptor (SXR)]. This activated PXR complex forms a heterodimer with retinoid X receptor (RXR), which binds to the xenobiotic-

Table 1: Common enzymes involved in metabolism of immunosuppressants

Metabolizing enzyme	*Drugs*	*Nature and process*
Cytochrome P450s (e.g., CYP 3A/5)	Cyclosporine (CsA)	Substrate, inhibitor
	Sirolimus (SIR)	Substrate, inhibitor
	Tacrolimus (TAC)	Substrate
UDP-glucoronyl transferase	MMF	Substrate
Xanthine oxidase	Azathioprine (AZA)	Substrate

Table 2: CYP3A substrates, inhibitors, inducers, and activators

Drug category	*Effect on CYP3A*	
Anticancer drugs	Busulfan (S)	Tamoxifen (S)
	Docetaxel (S)	Vinblastine (S, I)
	Doxorubicin (S)	Vincristine (S, I)
	Etoposide (S)	Vindesine (S)
	Paclitaxel (S)	
Immunosuppressants	Cyclosporine (S, I)	
	Methylprednisolone (I)	
	Sirolimus (S, I)	
	Tacrolimus (S)	
Antibiotics/antifungal agents	Clarithromycin (S)	
	Clotrimazole (I)	
	Erythromycin (S, I)	
	Itraconazole (S, I)	
	Ketoconazole (S, I)	
Antiretroviral agents	Amprenavir (S, I)	
	Indinavir (S, I)	
	Nelfinavir (S, I)	
	Ritonavir (S, I)	
	Saquinavir (S, I)	
Other cytotoxic drug	Colchicine (S)	
Hormonal agents	Cortisol (S)	Hydrocortisone (S)
	Dexamethasone (S, I)	Progesterone (S, I)
	Estradiol (S, I)	Testosterone (S, A)
Cardiac agents	Amiodarone (S)	Nicardipine (S, I)
	Atorvastatin (S)	Nifedipine (S, I)
	Digitoxin (PS)	Nitrendipine (S, I)
	Diltiazem (S, I)	Pravastatin (S)
	Felodipine (S)	Quinidine (S, I)
	Fluvastatin (S)	Simvastatin (S)
	Lidocaine (S)	Verapamil (S, I)
	Lovastatin (S)	

S, substrates; I, inhibitors; In, inducers; A, activators

responsive enhancer module (XREM) region of the CYP3A4 gene. This leads to genetic transcription, with increased production of CYP3A4, increasing its ability to metabolize various molecules, such as cyclosporine A (Fig. 1). Therefore, in patients who are given phenytoin, CsA levels are reduced as the rate of CsA metabolism is increased.[11] In transplant recipients, a reduction in CsA levels increases the risk of graft rejection. Erythromycin, on the other hand, is a known inhibitor of CYP3A. Thus, when erythromycin and CsA are coadministered, CsA metabolism is reduced and plasma concentrations of CsA increase.[12] This can result in toxicity from increased exposure to high CsA blood levels.

Drug Transporters with Immunosuppressants

Drug transporters play a significant role in the absorption, distribution, and elimination of immunosuppressants. Thus, modulation of transporter activity represents another mechanism by which these drugs can interact with one another as well as with other classes of agents. Recent studies have identified a number of drug transporters, the most prominent being P-glycoprotein (P-gp), the protein product of the multidrug resistance 1 gene (MDR1). CsA and TAC are P-gp substrates. In addition, depending upon the duration of exposure, CsA, TAC, and SIR have been shown to inhibit and induce P-gp. Other transporters, such as the multidrug resistance gene 2/3, the organic anion transporter proteins, the multidrug resistance-related proteins, and the sister of P-glycoprotein may modulate immunosuppressant action; however, further investigation is required. P-gp transports drugs from the intracellular portion of the cell to the extracellular portion. It is thought to provide a barrier function and help to excrete toxins from the body. P-gp is expressed on a variety of normal tissues, primarily in those with secretory or barrier functions: liver, intestine, kidney, the blood-brain barrier, and lymphocytes.[10,13] In these tissues, P-gp transports drugs out of the organ or cell and is therefore thought to provide a protective function for the organism. P-gp acts as an export pump that extrudes drugs from the intracellular compartment to the extracellular compartment. When P-gp activity is inhibited, more drug is available to distribute to the systemic circulation. In other words, the bioavailability of a given drug is increased in the presence of a P-gp inhibitor. St. John's wort has been shown to induce P-gp.[14] Since CsA is a P-gp substrate, the coadministration of St. John's wort and CsA results in a reduction in the systemic concentration of CsA. Coadministration of quercetin, an inhibitor of CYP3A4 and a modulator of P-gp, and oral CsA was shown to reduce the bioavailability in animal studies.[15] Verapamil, on the other hand, is an inhibitor of CYP3A and P-gp. The coadministration of verapamil and everolimus resulted in increased bioavailability of everolimus (Table 3).[16]

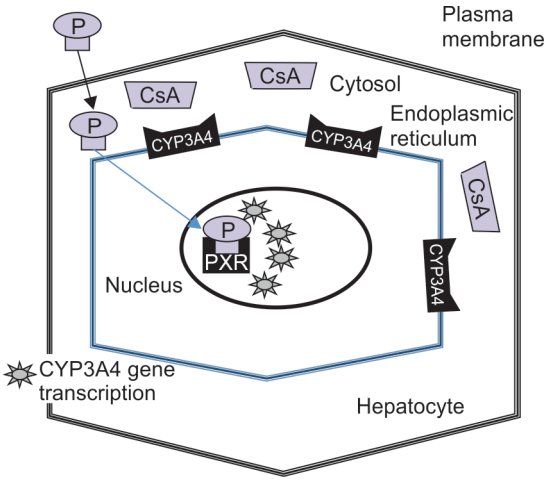

Fig. 1: Phenytoin induction of CYP3A4. P, phenytoin molecule; PXR, pregnane X receptor

Interactions between Antibacterial Agents and Immunosuppressants

The major interactions between antibacterial and immunosuppressants are discussed below. Minor interactions are summarized in Table 4.

Table 3: P-glycoprotein (P-gp) substrates, inhibitors, inducers, and activators

Drug category	*Effect on P-gp*	
Anticancer drugs	Actinomycin D (S)	Methotrexate (S, In)
	Cisplatin (S, In)	Mitomycin (S)
	Cytarabine (S)	Paclitaxel (S)
	Daunorubicin (S, In)	Taxol (S)
	Docetaxel (S)	Tamoxifen (I, In)
	Doxorubicin (S, In)	Vinblastine (S, I, In)
	Etoposide (S, In)	Vincristine (S, In)
	Fluorouracil (S, In)	Vindesine (S)
Immunosuppressants	Cyclosporine (S, I, In)	
	Methylprednisolone (S)	
	Prednisolone (S, In)	
	Sirolimus (I, In)	
	Tacrolimus (S, I, In)	
Antibiotics and antifungal agents	Clarithromycin (I)	
	Clotrimazole (In)	
	Erythromycin (S, I, In)	
	Itraconazole (S, I)	
	Ketoconazole (I)	
	Sparfloxacin (S)	
Antiretroviral agents	Amprenavir (S, In)	
	Indinavir (S)	
	Nelfinavir (S, I, In)	
	Ritonavir (S, I, In)	
	Saquinavir (S, I)	
Other cytotoxic drugs	Colchicine (S, In)	
	Mitoxantrone (S, In)	
Hormonal agents	Aldosterone (S)	Hydrocortisone (S, I)
	Cortisol (I)	Insulin (In)
	Dexamethasone (S, In)	Progesterone (I)
	Estradiol (In, MS)	Testosterone (I)
Cardiac agents	Amiodarone (I, In)	Nicardipine (I, In)
	Atorvastatin (I)	Nifedipine (In)
	Celiprolol (S)	Nitrendipine (I)
	Digoxin (S)	Quinidine (S, I)
	Diltiazem (S, I, In)	Talinolol (S)
	Felodipine (I)	Terfenadine (I)
	Lidocaine (I)	Verapamil (S, I, In)

S, substrates; I, inhibitors; In, inducers; A, activators

Table 4: Minor interactions between antibacterials and immunosuppressants

Antimicrobial	*Immunosuppressant*	*Severity of interaction*	*Interaction*	*Suggested action*
Fluoroquinolones				
Ofloxacin	CsA, TAC	++	↑ Imm level	Choose alternative
Ciprofloxacin	CsA, TAC	±	May ↑ Imm level	No adjustment/consider monitoring Imm levels
Levofloxacin	CsA		May ↑ CsA level	No adjustment/consider monitoring Imm levels
Moxifloxacin	CsA, TAC, SRL, EVR	–	None	No adjustment
Macrolides				
Erythromycin	CsA, TAC, SRL, EVR	+++	↑ Imm level	Avoid
Clarithromycin	CsA, TAC, SRL, EVR	+++	↑ Imm level	Avoid/↓ Imm by ½
Telithromycin	CsA, TAC, SRL, EVR	+++	↑ Imm level	Avoid
Aminoglycosides				
Gentamicin, Tobramycin, Amikacin, Streptomycin	CsA, TAC	+++	Enhanced nephrotoxicity	Avoid/monitor Imm levels and renal function
Rifamycins				
Rifabutin	CsA TAC, SRL, EVR	++	↓ Imm levels	Monitor Imm levels
Rifapentine[5]	CsA, TAC, SRL, EVR, Prednisone	++	↓ Imm levels	Monitor Imm levels
Rifampin	CsA, TAC, SRL, EVR, MMF, ECMS	+++	↓ Imm levels	Avoid/monitor Imm levels
Other antibacterials				
Nafcillin	CsA, TAC, SRL, EVR			Monitor Imm levels
Quinupristin/dalfopristin	CsA	+++	↑ CsA	Monitor Imm levels
Linezolid	MMF, ECMS, AZA	++	Myelosuppression	Monitor WBC and platelets
Sulfonamides	MMF, ECMS, AZA	++	Myelosuppression	Monitor WBC, hematocrit, platelets, and renal function
	CsA, TAC	++	Nephrotoxicity	Monitor WBC, hematocrit, platelets, and renal function
Tetracycline[6]	CsA, TAC, SRL, EVR	+	↑ Imm levels	Monitor Imm levels
Tigecycline	CsA	+	↑ Imm levels	Monitor Imm levels
Metronidazole	CsA, TAC, SRL, EVR	±	May ↑ Imm levels	No adjustment/consider monitor levels
Chloramphenicol (intravenous)	CsA, TAC, SRL, EVR	++	↑ Imm levels	↓ CsA or TAC by 25%
Clindamycin	CsA, TAC, SRL, EVR	±	May ↓ Imm levels	No adjustment/consider monitoring levels

Imm, immunosuppressants; CsA, cyclosporine; TAC, tacrolimus; SRL, sirolimus; EVR, everolimus; MMF, mycophenolate mofetil; ECMS, enteric-coated mycophenolate sodium; AZA, azathioprine (data on EVR not always present, but included in table on basis of the similar route of metabolism to other immunosuppressants involved in drug–drug interactions)

Macrolides

Commonly used macrolides are azithromycin and clarithromycin; erythromycin, being an old agent, is used rarely. These agents are commonly used for treatment of atypical pneumonia caused by *Legionella* spp., *Chlamydophila pneumonia*, or *Mycoplasma pneumonia* and enteritis due to Campylobacter spp. Erythromycin is sometimes used as a prokinetic agent in gut motility disorder.

Erythromycin and clarithromycin are moderate to strong inhibitors of CYP3A4, while azithromycin has minimal effect on CYP3A4; thus, erythromycin and clarithromycin decrease the metabolism of calcineurin inhibitors (CsA, TAC) and mTOR inhibitors (SRL, EVR). There is thus 3- to 10-fold rise in the immunosuppressant levels, when these drugs are given concomitantly. The effect of erythromycin or clarithromycin is less when given orally.[17] Erythromycin and clarithromycin also increase the absorption of CsA, by inhibiting its intestinal wall metabolism. If the combination is used, then at least 35–50% dose reduction of the immunosuppressant should be done; and daily drug level monitoring for calcineurin inhibitors and 72-hourly drug levels monitoring for mTOR inhibitors should be done.

There is no major pharmacokinetic interaction between azithromycin and calcineurin inhibitors and mTOR inhibitors, though there are cases reporting elevated levels of CsA and TAC when coadministered with azithromycin. Intravenous azithromycin may increase CsA levels, through P-glycoprotein inhibition or competitive biliary excretion.[18,19] It will be appropriate to monitor the drug level of CsA and TAC, when given with azithromycin.

Quinolones

Commonly used quinolones are ciprofloxacin, levofloxacin, and moxifloxacin. Ciprofloxacin decreases levels of MMF by interfering with enterohepatic circulation and absorption.[20] Though levofloxacin does not increase the level of CSA, drug level monitoring is indicated.[21] Moxifloxacin has no interaction with calcineurin and mTOR inhibitors.[22]

Aminoglycosides

Aminoglycosides are nephrotoxic, and the nephrotoxicity is potentiated in presence of nephrotoxic immunosuppressants like CsA and TAC.[23,24] Renal function monitoring is indicated when they are used concurrently. If renal dysfunction develops, aminoglycosides are better avoided, or the dose should be adjusted according to the GFR or creatinine clearance. One important consideration while dosing the antimicrobials, which are renally excreted, is to continually adjust the doses to maximize efficacy and prevent toxicity.[25]

Antitubercular Drugs

In most of the antitubercular regimes, rifamycins are the mainstay. All the rifamycins are strong inducers of CYP3A4. Rifampicin stimulates metabolism of cyclosporine by the CYP3A4 isoenzyme, resulting in an increase in cyclosporine clearance. Rifampicin also decreases the absorption of cyclosporine by inducing its metabolism by gut wall. Both rifampicin and rifabutin decrease the plasma levels of calcineurin and mTOR inhibitors, leading to acute graft rejection.[26–29] This effect has been reported even with the concurrent use of multiple CYP3A4 inhibitors.[30] In presence of these agents, maintaining therapeutic levels of calcineurin and mTOR inhibitors is extremely difficult; hence, these combinations should be avoided. In cases where rifamycins can't be avoided for the treatment of tuberculosis, doses of immunosuppressive agents should be increased. Initially, the dose of calcineurin or mTOR inhibitors should be doubled. This should rapidly be increased with daily drug level monitoring till a stable dose has been achieved. Up to 10-fold increase in dose has been reported. Dose should be decreased with drug level monitoring, once rifamycins are discontinued. Rifapentine is a strong inducer of CYP3A4, but not much is known about this drug with regards to interaction with immunosuppressants.

Mycophenolate is metabolized into mycophenolic acid, which undergoes glucuronidation by uridine diphosphate glucuronosyltransferases (UGTs) in the liver, kidney, and intestine to its inactive metabolite (7-O-glucuronide). Rifampicin induces intestinal, kidney, and liver glucuronidation of mycophenolic acid by UGTs and reduces enterohepatic recirculation and absorption of mycophenolic acid. Also one metabolite of MMF, acyl-glucuronide, gets accumulated and attains higher blood level in presence of rifampicin, which may increase the toxicity or adverse effects. Hence in presence of rifampicin, its plasma level should be monitored, and the dose should be adjusted accordingly.[31] Rifampicin is a potent liver enzyme inducer, which increases the metabolism of the steroids, thereby reducing the effect of steroids by blood levels. Steroid dose should be increased initially, and should be gradually decreased, once rifampicin is discontinued.[32,33] Isoniazid and ethambutol do not seem to interact with immunosuppressive agents.

Other Antibacterials

- Renal toxicity of cyclosporine is increased by nafcillin, vancomycin, and alternative antibiotic should be used. Higher doses of trimethoprim-sulfamethoxazole potentiate the nephrotoxicity of calcinurin inhibitors (CNIs).[34]
- Co-amoxiclav changes the intestinal flora and may affect MMF absorption by enterohepatic circulation. Close vigilance is required when used with MMF.[20]
- Combination of norfloxacin with metronidazole (commonly used to treat dysentery on OPD basis) decreases MMF levels by affecting the enterohepatic circulation. Drug level monitoring of MMF is suggested.[35]
- Dalfopristin/quinupristin are inhibitors of CYP3A4 and increase the blood levels of calcineurin inhibitors. Drug level monitoring is therefore advised. Calcineurin inhibitors and MMF increase the arthralgia and myalgia caused by dalfopristin/quinupristin inhibitors, through pharmacodynamic interaction.[36]

Interactions between Antifungal Agents and Immunosuppressants

Azoles, echinocandins, and polyenes are all used in transplant recipients. These are summarized in (Table 5).

Azoles

All azoles are inhibitors of CYP3A4 with differing potency. In order of decreasing potency, they are ketoconazole (most potent), itraconazole and posaconazole (more potent than), fluconazole, voriconazole, and isavuconazole.[37] They all decrease the metabolism of calcineurin and mTOR inhibitors. Ketoconazole has often been used along with calcineurin or mTOR inhibitors to decrease the dose of immunosuppressant and to decrease the cost for transplant.[38–40] Voriconazole increases CsA and TAC levels (increase in AUC levels by 70 and 221%, respectively), and it is recommended to decrease the doses of CSA and TAC by 50 (half) and 33% (one-third), respectively.[37,41] Voriconazole increases the level of sirolimus up to 10-fold (increase in AUC by 1014%) and thus, they can be safely administered together provided a specific protocol is used.[42] Similarly, everolimus should be used with caution with voriconazole.[43]

Posaconazole, like voriconazole, too increases the levels of calcineurin and mTOR inhibitors and requires empiric dose reduction of CsA to three-fourth of the normal dose and TAC to one-third of the normal dose.[44,45] Posaconazole should not be administered with sirolimus as it increases its blood level by ninefold.[46,47] Not much of data are available on posaconazole administered with everolimus, though one case report found 3.8-fold increase in everolimus levels. Still, posaconazole in contraindicated with everolimus.[44,45] Posaconazole increases MMF levels due to inhibition of P-glycoprotein. The MMF levels should be monitored when used with posaconazole.[47] Even after dose adjustment, drug levels of immunosuppressants should be monitored frequently when used with voriconazole or posaconazole.[47,48]

The interaction of fluconazole with immunosuppressants is both drug-dependent and dose-dependent. At lower doses (100–200 mg/day), CsA levels are not altered but there is moderate to significant increase in TAC levels. As higher doses as used in systemic candidiasis (400 mg/day), significant dose reduction for CSA and TAC is needed, guided by drug level monitoring.[49] Fluconazole also increases trough levels of sirolimus and everolimus; dose reduction and drug level monitoring are required.[49,50] Isavuconazonium sulfate, a prodrug of the broad-spectrum azole isavuconazole, was approved by the U.S. FDA, in 2015, for the treatment of invasive aspergillosis and mucormycosis. Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inhibitor of UGTs. It has been shown to increase the drug level of CsA, tacrolimus, and serolimus. Thus, its effects are less than other azoles and it can be used in patients on immunosuppressants, with drug level monitoring.[51]

Oral clotrimazole lozenges (for prophylaxis of oral mucocutaneous candidiasis) has been shown to increase the

Table 5: Interactions between antifungal agents and immunosuppressants

Antifungals	*Immunosuppressant*	*Severity of interaction*	*Interaction*	*Suggested action*
Azoles				
Ketoconazole	CsA, TAC, SRL, EVR	+++	↑ Imm levels	Avoid/↓ Imm by 1/2
Voriconazole	CsA, TAC, SRL, EVR	+++	↑ Imm levels	↓ CsA by 1/2, ↓ Tac by 2/3
Itraconazole	CsA, TAC, SRL, EVR	++	↑ Imm levels	Monitor Imm levels
Posaconazole	CsA, TAC, SRL, EVR	+++	↑ Imm levels	↓ CsA by 1/4, ↓ Tac by 2/3
Fluconazole	CsA, TAC, SRL, EVR	++	↑ Imm levels	Dose-dependent ↓ CsA and Tac by 1/3
Clotrimazole	CsA, TAC, SRL, EVR	++	↑ Imm levels	Monitor Imm levels
Polyenes				
Amphotericin and lipid formulations of amphotericin	CsA, TAC	++	Nephrotoxicity	Monitor Imm levels and renal function
Echinocandins				
Caspofungin	TAC	±	May ↓ TAC levels	None
	CsA	++	↑ Caspofungin levels	Monitor AST/ALT
	MMF (no data on ECMS)	–	None	None
	No data on SRL, EVR			
Micafungin	TAC, MMF, Prednisone (no data on ECMS)	–	None	None
	CsA	++	↓ CsA levels	Monitor Imm levels
	SRL (no data on EVR)	++	↑ SRL levels	
Anidulafungin	CsA	+	↑ Anidulafungin levels	None
	TAC	–	None	None
	No data on SRL, EVR			

Imm, immunosuppressant; CsA, cyclosporine; TAC, tacrolimus; SRL, sirolimus; EVR, everolimus; MMF, mycophenolate mofetil; ECMS, enteric-coated mycophenolate sodium; AZA, azathioprine (data on EVR not always present, but included in table on basis of similar route of metabolism to other immunosuppressants involved in drug–drug interactions)

levels of TAC up to twofold through CYP3A4 inhibition. The CNI or mTOR inhibitor levels should be monitored when used with oral clotrimazole.[52,53]

Echinocandins

Echinocandins are widely used now in immunosuppressed patients as an alternative to azoles. All echinocandins are available only in intravenous formulation. Echinocandins are not significantly metabolized by CYP3A4; and none is a major P-glycoprotein substance, hence they have minimum interaction with the immunosuppressant.[54] The original studies that led to approval of caspofungin had shown increased hepatotoxicity with concurrent use of caspofungin and CsA. CsA also increases AUC for caspofungin by almost 35%.[55] One more study found that AUC for TAC is decreased by 20% in presence of caspofungin.[56] Subsequent studies, however, didn't find any significant increase in hepatotoxicity or in the drug levels of CsA and tacrolimus in the presence of caspofungin.[57,58] Current recommendation is to follow the standard dose and drug level monitoring of both CsA and tacrolimus when used with caspofungin.[55] CNIs do not have any interaction with the metabolites of MMF too. Anidulafungin has minimal pharmacokinetic interaction with CsA and no interaction with tacrolimus; hence, no dose modification for either drug is needed, when used concurrently.[59,60] No data are available on interaction between mTOR inhibitors and caspofungin or anidulafungin. Micafungin doesn't have any pharmacokinetic interaction with calcineurin inhibitors, MMF, or prednisone, but in one study it caused decreased blood levels of CsA in healthy volunteers, by 16%, hence CsA level monitoring is suggested.[61,62] Micafungin has been found to increase sirolimus AUC by 21% and hence dose adjustment and drug level monitoring are suggested[61]

Polyenes

Amphotericin-B is the polyene used in invasive mycoses. The most important dose-limiting side effect of amphotericin-B is nephrotoxicity. Calcineurin inhibitors too have nephrotoxicity and their concurrent use with amphotericin-B increases renal toxicity. Vigilant monitoring of renal function is recommended. Lipid formulations of amphotericin-B are less nephrotoxic than amphotericin-B deoxycholate and are the preferred agents for patients on calcineurin inhibitors.

Interactions between Antiviral Agents and Immunosuppressants

Most severe interactions occur between the antiretroviral agents (protease inhibitors) and immunosuppressants.

Interactions with Antiretroviral Agents

Patients infected with HIV-1 virus are being increasingly transplanted for organ failures.[63] Accordingly, more incidences of interactions with immunosuppressants and antiretroviral drugs had been coming up. Most of the antiretroviral drugs are inhibitors of CYP3A4 and p-glycoprotein and have to be cautiously used with CNIs and mTOR inhibitors.

Protease Inhibitors (PI)

Patients receiving PIs require significant dose reduction of both calcineurin and mTOR inhibitors, to maintain a safe trough level. Lopinavir and ritonavir combination has shown 10-fold increase

in the half-life of TAC.[63] Case reports in kidney transplant patients receiving saquinavir or darunavir showed an increase in the tacrolimus trough level, leading to 96.5% reduction in the dose of tacrolimus.[64,65] Even with cyclosporine dose was reduced by almost 85% in patients receiving nelfinavir and indinavir.[66,67] Same interactions have been seen between sirolimus and PIs. There is not much data on everolimus with protease inhibitors, though the product monograph suggests avoiding everolimus with PIs.[68]

Nucleotide Analogs

Tenofovir has renal toxicity, which may increase when combined with tacrolimus. Though there is no pharmacokinetic interaction between tenofovir and calcineurin inhibitors. Mycophenolate mofetil is metabolized through uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) pathway; similarly, abacavir and zidovudine are metabolized by the same pathway. Hence, MMF levels should be monitored when used with these two nucleotide analogs.[69]

Other Antiretroviral Agents

Efavirenz, nevirapine, and etravirine have been associated with decreased levels of CsA, tacrolimus, and sirolimus due to induction of CYP3A4. Drug level monitoring and dose modification are suggested. Delavirdine is an inhibitor of CYP3A4 and has potential to increase the levels of immunosuppressants. Drug level monitoring is indicated.[69]

Other Antivirals

Nephrotoxicity of calcineurin inhibitors is increased in presence of cidofovir, foscarnet, and intravenous acyclovir. Ganciclovir and leflunomide cause myelosuppression. Regular white blood cell count and platelets count should be done while on immunosuppressants (Table 6).[64]

Table 6: Interactions between antivirals and immunosuppressants

Antivirals	*Immunosuppressant*	*Severity of interaction*	*Interaction*	*Suggested action*
Antiviral agents—non-HIV				
Acyclovir	MMF, ECMS	±	↑ ACV, ↓ MPA	None
I.V. Acyclovir	CsA, TAC	+++	Nephrotoxicity	Monitor renal function
Valacyclovir	MMF, ECMS	±	↓ MPA	None
Ganciclovir	MMF, ECMS, AZA	++	Neutropenia	Monitor WBC
Valganciclovir	MMF, ECMS, AZA	++	Neutropenia	Monitor WBC
Foscarnet	CsA, TAC	+++	Nephrotoxicity	Monitor renal function, Ca, Mg
Cidofovir	CsA, TAC		Nephrotoxicity	Monitor renal function
Acyclovir	MMF, ECMS	±	↑ ACV, ↓ MPA	None
I.V. Acyclovir	CsA, TAC	+++	Nephrotoxicity	Monitor renal function
Valacyclovir	MMF, ECMS	±	↓ MPA	None
Ganciclovir	MMF, ECMS, AZA	++	Neutropenia	Monitor WBC
Oseltamivir	CsA, TAC, MMF	±	13% increase in TAC trough only	Monitor Imm levels
	SRL	–	None	
	No data with ECMS, EVR			
Zanamivir	CsA, TAC, SRL, EVR			
MMF, ECMS	–	None	None	
Leflunomide	MMF, ECMS, AZA, SRL, EVR	+++	Myelosuppression	Hold MMF, ECMS, AZA and monitor WBC, hematocrit, and platelets
Antiretroviral agents—NNRTIs				
EFV	CsA, TAC, SRL, EVR	++	↓ CsA, ↓ TAC	Monitor Imm level
NVP	CsA, TAC, SRL, EVR	±	May ↓ Imm level	Monitor Imm level
ETR	CsA, TAC, SRL, EVR	±	May ↓ Imm level	Monitor Imm level
DLV	CsA, TAC, SRL, EVR	++	↑ Imm level	Monitor Imm level
Antiretroviral agents—PIs				
ATV, DRV, FPV, IDV, LPVr, NFV, RTV, SQV, TPVr	CsA, TAC, SRL, EVR not recommended for use with RTV regimens	+++	↑ CsA ↑ TAC/SRL/EVR	CsA 25–50 mg daily TAC 1 mg once or twice a week SRL 1 mg once or twice a week When using RTV-PI boosted regimen TPVr interaction unpredictable
Antiretroviral agents—NRTIs				
ZDV	MMF/ECMS	+	None	
D4T	MMF/ECMS	+	None	

Imm, immunosuppressant; CsA, cyclosporine; TAC, tacrolimus; SRL, sirolimus; EVR, everolimus; MMF, mycophenolate mofetil; ECMS, enteric-coated mycophenolate sodium; AZA, azathioprine (Data on EVR not always present, but included in table on basis of similar route of metabolism to other immunosuppressants involved in drug–drug interactions.); NNRTIs, non-nucleoside reverse transcriptase inhibitors: DLV, delavirdine; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; NRTIs, nucleoside reverse transcriptase inhibitors: AZT, zidovudine; D4T, stavudine (none of the NRTIs are expected to interact with CsA, TAC, SRL, EVR); PIs, protease inhibitors: ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; IDV, indinavir; LPVr, lopinavir + ritonavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPVr, tipranavir + ritonavir; ZDV, Ziovudine

Interactions between Antimalarial Drugs and Immunosuppressants

Artemether/lumefantrine is a new antimalarial drug. Artemether is an inducer of CYP3A4 and it has the potential to decrease the levels of CNIs and mTOR inhibitors. Drug levels should be monitored while patient is on artemether/lumefantrine.[70]

Conclusion

Immunosuppression plays a vital role in improving graft survival and has improved patient outcomes significantly over the 50 years. Infections with either bacteria, fungi, viruses, or parasites are the most common complication of immunosuppression. Significant interactions occur between immunosuppressants and antimicrobials. Therefore, appropriate dosing and delivery of antimicrobials in these patients is a major challenge. Modulation of cytochrome P450 3A4 and drugs transporters such as P-gp may alter the blood levels of both antimicrobials and immunosuppressants causing alteration in organ function, ineffective immunosuppression, etc. Careful choice of antimicrobials and therapeutic drug level monitoring are essential aspects to improve the outcomes in these patients.

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