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Drug Interactions and Safe Prescription Writing for Liver Transplant Recipients

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Immunosuppression optimization is central to graft function in liver transplant recipients. Post-transplantation patients develop new onset or worsening metabolic syndrome, are prone to atypical infections, and are at higher risk of developing cardiac and brain-related clinical events. In this context, liver transplant recipients are at risk of using multiple comedications alongside immunosuppressants. It is imperative for the transplant physician to understand the various drug–drug interactions that potentially reduce or promote toxicity of immunosuppression, as well as associated synergistic or antagonistic effects on extrahepatic organ systems. This comprehensive review discusses drug–drug interactions in liver transplant recipients and the impact and role of complementary and alternative medicines among individuals on immunosuppression. (J Clin Exp Hepatol xxxx;xxx:xxx)

Liver transplantation has grown by leaps and bounds since the first successful liver transplant by Thomas Starzl in 1967.[1] A breakthrough in the evolution of liver transplantation was the emergence of immunosuppressive agents. In the early days, using azathioprine with steroids gave about a 60% one-year survival rate. With the introduction of cyclosporine, an 80% graft survival rate could be achieved in one year.[2,3] The true game changer was the introduction of FK506, or Tacrolimus, approved for use in 1994 for transplant recipients.[4] The Tacrolimus versus microemulsified Cyclosporin (TMC) randomized control trial in 2002 gave conclusive evidence to show that Tacrolimus was better than cyclosporin at multiple endpoints, including graft and patient survival at one year, thus establishing it as the main immunosuppressant in liver transplant recipients.[5] Mycophenolate mofetil (MMF) was also introduced at about the same time and, in combination with cyclosporine and steroids, was more effective in preventing acute rejection than Azathioprine.[6–8] A late addition to the armamentarium was the mammalian target of rapamycin (mTOR) receptor inhibitors such as Sirolimus and its latest variant, Everolimus.[9]

Tailoring immunosuppression in the post-transplant period continues to be a challenging activity. The genetic polymorphism observed with cytochrome P450 (CYP-450) isoenzyme and P-glycoprotein, involved in the metabolism of these drugs, produces significant inter-patient variability in drug levels.[10–12] In addition, intra-patient variability due to altered therapeutic levels owing to a multitude of drug interactions is an ever-present problem. All these factors mandate close therapeutic drug monitoring to ensure adequate levels of drugs in the blood and to prevent pharmacokinetic and pharmacodynamic drug interactions.

Liver transplant recipients are maintained on lifelong immunosuppression to reduce the risk of allograft rejection/dysfunction. This increases the risk of developing an opportunistic infection due to reduced immune response. An optimal immunosuppressive regimen must be personalized to each, balancing the risk of rejection with its potential side effects.[13] The bioavailability of drugs is often measured by quantifying the area under the curve (AUC). Most commonly in solid organ transplant recipients, corticosteroid-based induction immunosuppression is used. A combination of calcineurin inhibitors (CNIs, e.g., Tacrolimus or Cyclosporine), antiproliferative agents (mycophenolic acid (MPA) prodrugs or Azathioprine), and steroids is the commonly used regimen for maintenance immunosuppression.[14] Steroids are often withdrawn early to avoid known side effects. Most liver transplant recipients are on a single CNI for one year. Convincing data emerging in recent years has shown that Basiliximab-based, steroid-free induction immunosuppression has similar a graft and patient survival along with a reduced incidence of metabolic complications.[15] This

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Abbreviations: AZA: azathioprine; CAM: complementary and alternative medicine; CNI: calcineurin inhibitors; CYP: cytochrome P-oxidase family; MMF: mycophenolate mofetil; MPA: mycophenolic acid; mTOR: mammalian target of Rapamycin; PPI: proton pump inhibitor

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comprehensive review discusses drug–drug interactions in the background of immunosuppressants in liver transplant recipients by providing succinct data from the published literature. We also discuss the impact and role of complementary and alternative medicines among individuals on immunosuppression.

A BRIEF OVERVIEW OF POST-LIVER TRANSPLANT IMMUNOSUPPRESSION

Calcineurin Inhibitors (CNI) and mTOR Inhibitors

Calcineurin inhibitors such as Cyclosporin and Tacrolimus form the foundation on which post-transplant immunosuppression is based in current clinical practice. Although chemically distinct molecules, they work by inhibiting the production of interleukin (IL)-2 inside T cells.[16] Being lipophilic, they are easily absorbed through the gut. However, due to extensive first-pass metabolism, the bioavailability could be better and highly variable. P450 (CYP) 3 A, a member of the CYP-450 isoenzyme family, is responsible for the metabolism of CNIs and mTOR inhibitors.[17] Specifically, the CYP3A4 and CYP3A5 enzymes are responsible for the most CNI clearance. Similarly, the mTOR inhibitors (Sirolimus, Everolimus) undergo first-pass metabolism by the CYP3A4 and CYP3A5 systems. The isoenzyme CYP 2C8 is additionally involved in the metabolism of mTOR inhibitors. In addition, drug transporters such as the efflux pump glycoprotein known as P-glycoprotein also play an important role in the metabolism of CNIs and mTOR inhibitors.[18,19] Due to this, any agents/drugs that inhibit CYP3A or P-glycoprotein can increase the bioavailability of CNIs and mTOR inhibitors and vice-versa for agents/drugs that induce CYP3A or P-glycoprotein. Reduced drug levels predispose patients to rejection and graft loss, whereas elevated levels can lead to drug toxicity. An elevated serum level of a calcineurin inhibitor is associated with nausea, headache, tremor, seizure, altered mentation, hypertension, and acute kidney injury. Increased levels of MMF or azathioprine are generally well tolerated but have been reported to result in leukopenia or pancytopenia. Clinically significant interactions typically occur with calcineurin and mTOR inhibitors. The major drugs known as inducers and inhibitors of CYP3A are elaborated in Table 1.

Table 1 Commonly Used Drugs Causing Interactions with Immunosuppressants.

Cytochrome P 450 enzyme related	
Inhibitors[a]	**Inducers**[b]
Amiodarone	Phenytoin
Diltiazem	Fosphenytoin
Verapamil	Phenytoin
Clarithromycin	Phenobarbital
Erythromycin	Carbamazepine
Ketoconazole	Rifampicin
Itraconazole	Rifabutin
Posaconazole	
Voriconazole	
Fluconazole	
Isavucanazole	
Imatinib	
Cimetidine	
Grapefruit juice	
P-Glycoprotein related	
Inhibitors[a]	**Inducers**[b]
Amiodarone	Carbamazepine
Verapamil	Fosphenytoin
Carvediolol	Phenytoin
Azithromycin	Rifampicin
Erythromycin	Green tea
Clarithromycin	
Isavucanazole	
Ketoconazole	
Posaconazole	
Tamoxifen	
Ledipasvir	

[a]Drugs that inhibit P 450/P-gp cause an increase in the immunosuppressant concentration leading to toxicity.
[b]Drugs that induce P 450/P-gp cause decreased levels of immunosuppressant concentration and can lead to the rejection of transplanted organ.

Mycophenolate Mofetil

MMF is a prodrug converted to its active metabolite, MPA, after oral administration. It is an antiproliferative agent that inhibits inosine monophosphate dehydrogenase, thereby inhibiting the *de novo* purine synthesis needed for lymphocyte proliferation. MPA is metabolized by uridine diphosphate glucuronosyltransferase in the liver, gut, and kidney into MPA-glucuronide (MPAG).[20] It is strongly bound to albumin, and the free plasma MPA is the pharmacologically active form of the drug. The MPAG is excreted into the gut through the bile and absorbed back through enterohepatic circulation, ultimately excreted in the urine. Alterations in colonic bacteria, which could reduce enterohepatic circulation, could reduce exposure to MPA. Data also suggest that Cyclosporin could reduce exposure to MPA by inhibiting excretion into the bile. At the same time, Tacrolimus could increase the exposure by inhibiting glucuronosyltransferases.[21,22] Albeit not having any clear recommendations, therapeutic monitoring of MMF is not usually carried out.

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Azathioprine

Azathioprine (AZA) is a prodrug converted to 6-mercaptopurine, its active metabolite. Thiopurine methyl transferase is involved in the excretion of AZA. This enzyme is present in low levels or deficient in about 10% of the general population and may lead to myelotoxicity.[23] Testing for thiopurine methyl transferase mutation can identify patients at risk for toxicity from AZA use. A summary of the mode of action and metabolism of commonly used immunosuppression agents in liver transplant recipients is shown in Figure 1.

DRUG INTERACTIONS AND SAFE PRESCRIPTION OF DRUGS

Drug interactions can affect the pharmacokinetics of drugs and alter drug efficacy and toxicity. Drug interactions can be classified into pharmacokinetic and pharmacodynamic interactions.[24] Pharmacokinetic drug interactions refer to the alterations in a drug's pharmacokinetics parameters (absorptions, distribution, metabolism, and elimination) when another drug is introduced simultaneously. Pharmacokinetic drug interactions, therefore, alter the plasma drug concentration of the drug. On the other hand, pharmacodynamic interactions refer to the modulation of the effect of one drug by an offending drug. In this scenario, when a combination of drugs is started, there is an alteration of the dose–response relationship, which may, in turn, lead to either toxicity or ineffectiveness. As discussed, various interactions with commonly used drugs can result due to the pharmacokinetics of the immunosuppressants used in the post-transplant period. In the peri-operative period, it is essential to maintain the optimum therapeutic levels of crucial immunosuppressants to prevent the rejection of the newly implanted graft. On the other hand, an undesirable increase in the therapeutic levels of these drugs can expose the patient to an increased risk of toxicity and opportunistic infections. A balance is essential and desirable. We will discuss the drug–drug interactions between these various classes of drugs.

Antibiotics

Multiple classes of antibiotics are known to interact with the pharmacokinetics of immunosuppressants.

Macrolides

Newer macrolides such as Azithromycin and Clarithromycin are used to treat community-acquired pneumonia, skin infections, and upper respiratory tract infections. Its concomitant use with CNIs such as Tacrolimus leads to reduced metabolism of CNIs, increasing serum concentrations. Clarithromycin and Erythromycin (rarely used nowadays) are strong inhibitors of CYP3A and P-glycoprotein, increasing the Tacrolimus AUC by 3–7.5-fold.[25–27] Azithromycin, although not a potent inhibitor of CYP3A, does inhibit the transport protein that is P-glycoprotein. A 2- to 3-fold rise in Tacrolimus levels has been reported with its use.[28] Although not recommended for coadministration, reducing Tacrolimus to 50% is recommended if the clinical situation warrants it.[29] Levels must be closely monitored 1–3 days after the coadministration. A

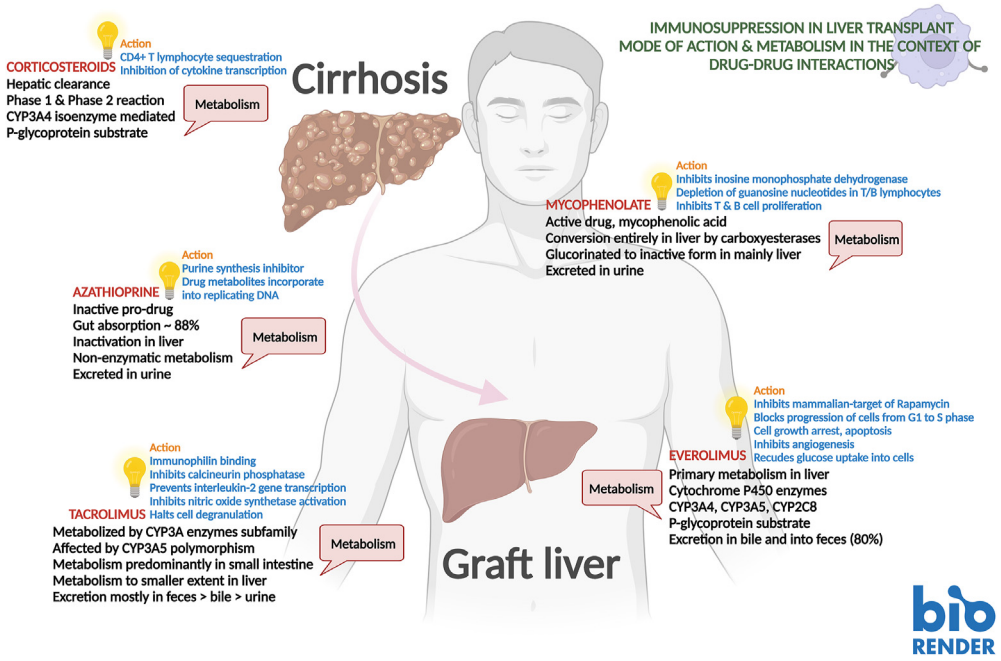

Figure 1 Summary of the mode of action and metabolism of commonly used immunosuppression medications in liver transplant recipients.

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combination of Clarithromycin or Erythromycin with mTOR inhibitors such as Everolimus is not recommended due to the many-fold rise in the AUC (>15-fold) seen in healthy subjects.[29,30]

Quinolones

Fluoroquinolones such as Levofloxacin, Ciprofloxacin, and Ofloxacin are commonly used in clinical practice as first-line antibiotics in commonly seen infections. These drugs prolong the QT interval by blocking voltage-gated potassium channels. Post-marketing studies in tacrolimus have also noted prolonged QT intervals in some patients.[31] When combining Levofloxacin with Tacrolimus, patients must be monitored for symptoms and signs of a prolonged QT interval and arrhythmias.[32] This is less so with Ciprofloxacin. However, being a weak inhibitor of CYP3A, close monitoring of Tacrolimus levels is necessary. Quinolones such as Ciprofloxacin have been reported to reduce the enterohepatic circulation of MMF and subsequently reduce blood levels.[33,34] Ofloxacin is not known to any major interactions with CNIs. None of the quinolones have any major interaction with mTOR inhibitors.

Antituberculosis Drugs

Developing countries continue to be burdened by tuberculosis. The traditional antitubercular regimen is based on Rifampicin. Being a strong inducer of CYP3A, Rifampicin and the newer antituberculosis drug, Rifapentine, (a moderate inducer) lead to the increased metabolism of Tacrolimus and corticosteroids, leading to sub-therapeutic levels and a consequent increase in the risk of rejection.[35–37] Up to 68% reduction in the AUC of Tacrolimus has been reported.[38] When coadministered, the Tacrolimus dose must be increased 2-fold along with closely monitoring levels.[29,39] Rifampicin increases the glucuronidation of MPA (the active metabolite of MMF) along with the increased biliary excretion of MPAG and reduces the enterohepatic circulation of mycophenolic acid. This leads to a reduction in the serum concentration of MMF.[39,40] Close monitoring is required in such scenarios. Other antitubercular drugs do not have significant interactions with immunosuppressants.

Nephrotoxic Antibiotics

An additive effect on nephrotoxicity is seen when CNIs are combined with antibiotics known to have nephrotoxic effects. Aminoglycosides are one such group of drugs that must be used cautiously or avoided completely in the immediate postoperative period and among those with compromised renal functions.[41]

To summarize, concomitant use of macrolide antibiotics with CNIs and mTOR inhibitors leads to the latter's reduced metabolism and increase in the serum concentration and risk of toxicity. Specifically, Clarithromycin or Erythromycin with mTOR inhibitors such as Everolimus is not recommended to the high risk of immunosuppression toxicity. Fluoroquinolones should be used cautiously along with Tacrolimus and MMF as they can lead to life-threatening QT-prolongation in the former and reduction in efficacy in the latter. Among antituberculosis drugs, Rifampicin and Rifapentine, strong inducers of CYP3A, reduce the levels of Tacrolimus and MMF drastically.

Antifungals

The role of antifungal drugs in the postoperative period after solid organ transplantation must be considered. They are extensively used in prophylaxis against opportunistic fungal infections. Azoles, echinocandins, and polyenes form the major antifungal drugs used in clinical practice.

Azoles

Azoles are potent inhibitors of CYP3A and lead to the decreased metabolism of CNIs and mTOR inhibitors. Ketoconazole is the most potent inhibitor, followed by Posaconazole, Fluconazole, Voriconazole, and Isavucanazole.[42] Coadministration of azoles leads to a significant increase in the bioavailability of CNIs and mTOR inhibitors. The concurrent use of azoles and Tacrolimus is associated with a marked reduction in the Tacrolimus requirement and has been used by many clinicians as a cost-reducing modality.[43,44] Fluconazole is associated with up to 60% reduction in the Tacrolimus dose when administered together. This mechanism is dose- (an increased effect with higher Fluconazole) and route-dependent (no major impact of intravenous tacrolimus). The longer half-life (>1 day) of Fluconazole means that this effect is preserved for up to 4–5 days after stopping Fluconazole.[45] Voriconazole and Posaconazole are used in specific clinical scenarios after liver transplants. Both are strong inhibitors of CYP3A, and a modification of tacrolimus to one-third of the original dose is advised.[46,47] The newer azole, Isavuconazole, which finds clinical relevance in certain situations, is a P-glycoprotein inhibitor (and a weak CYP3A inhibitor) and, similar to other azoles, can increase the trough levels of Tacrolimus.[48]

Echinocandins

Commonly used echinocandins are Anidulafungin, Caspofungin, and Micafungin. These drugs are not modifiers of the CYP3A enzyme or P-glycoprotein activity.[49] No major drug interactions exist between them and immunosuppressants. However, isolated reports of elevation in the transaminases when cyclosporine is coadministered with Caspofungin exist.[50]

Polyenes

Amphotericin B, used in treating invasive mycoses, is known to be nephrotoxic. The lipid formulation, however, is reported to be less nephrotoxic. The additive effect of nephrotoxicity can occur when administered

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concurrently, which mandates close monitoring of the renal function.[24]

To summarize, azoles such as Ketoconazole and Fluconazole increase levels of CNIs and mTOR inhibitors, and their use warrants a reduction in immunosuppression to prevent toxicity. Echinocandins such as Anidulafungin, Caspofungin, and Micafungin do not interact with CNIs or mTOR inhibitors. In contrast, polyenes such as Amphotericin-B do not have a direct impact on the levels of immunosuppression but can be synergistic in promoting nephrotoxicity.

Anticonvulsants

Antiseizure medications are very often used in a post-liver transplant. The most used drug is Phenytoin. Phenytoin is a strong inducer of CYP3A, and studies indicate a significant reduction in the blood levels of CNIs following coadministration.[51,52] It is recommended to increase the dose of CNIs by 2-fold if both drugs need to be simultaneous. It is interesting to note that clinicians have used this property of Phenytoin to enhance the tacrolimus elimination in the case of toxicity.[53–56] Like phenytoin, other anticonvulsants such as Carbamazepine and Phenobarbital are also strong inducers of CYP3A, producing similar effects on CNIs and mTOR inhibitors. The newer anticonvulsant, Levetiracetam, is now gaining popularity in post-liver transplant settings owing to a lack of drug interactions.[24]

Antihypertensive Medications

Several studies have reported that more than 50% of patients after a liver transplant develop systemic hypertension requiring medical management.[57] Systolic blood pressure can be elevated by 40–50 mm Hg in the postoperative period after liver transplantation, possibly due to systemic vasoconstriction. In addition, CNIs induce hypertension via endothelin-mediated vasoconstriction, decreased nitric oxide production, and increased renal tubular reabsorption.[58] The commonly used beta-blockers, such as Metoprolol, do not generally have any interaction with immunosuppressants.[24] However, Carvedilol may increase Cyclosporine's blood levels.[59] Non-dihydropyridine calcium channel blockers such as verapamil and diltiazem can help establish a normal sinus rhythm in the postoperative period. Both these drugs are moderate inhibitors of CYP3A and consequently require a reduction in the dose of CNIs and mTOR inhibitors.[60,61] Most dihydropyridine calcium channel blockers, except Nifedipine and Nicardipine, do not exhibit this interaction and can be safely used. Nifedipine decreased the daily and cumulative dosage requirement of tacrolimus; hence, it is recommended that the blood concentrations of tacrolimus be monitored during the coadministration of these drugs.[26] Amlodipine has been reported to increase the AUC of Tacrolimus by 2.4- to 4-fold in volunteers.[62] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers do not significantly interact with immunosuppressants used in liver transplant recipients.

Antiviral Drugs

Direct-acting Antivirals for Chronic Hepatitis C

One of the common indications for a liver transplant in the Asian population is hepatitis C virus (HCV). Anti-HCV medications are expected to be continued post-transplant in most cases. Most commonly, Sofosbuvir alone or combined with Sofosbuvir/Ledipasvir is used. Data regarding interaction with CNIs are conflicting.[63] Reduced tacrolimus levels, when combined with Sofosbuvir-containing regimens, are found in many studies.[64] Whether this results from the interaction or improvement in the liver function due to the treatment of HCV leading to increased metabolism of Tacrolimus is contentious. Immunosuppressant interactions with newer direct-acting antivirals such as Velpatasvir, Elbasvir/Grazoprevir, Glecaprevir/Pibrentasvir, and Voxilaprevir are identified as minimal in nature and with good safety of margin for use in the post-liver transplant period. These drugs can also be safely combined with mTOR inhibitors, Azathioprine, and Mycophenolate. Nonetheless, other medications could interact, nonetheless insignificantly, with direct-acting antivirals prescribed for HCV infection in the post-liver transplant period. For example, combining sofosbuvir with a second direct-acting antiviral is contraindicated in concomitant use with amiodarone due to the risk of severe symptomatic bradycardia. It is therefore strongly recommended that concomitant medications be reviewed using the University of Liverpool's Hepatitis Drug Interactions website, available at https://www.hep-druginteractions.org/checker. On a side note, regarding antiviral drugs used for chronic hepatitis B virus infections, such as Lamivudine, Entecavir, and Tenofovir, no significant drug–drug interactions were notable with immunosuppressants in the post-liver transplant period.

Antiretroviral Drugs for Human Immunodeficiency Virus

Protease inhibitors form the backbone of the current treatment of human immunodeficiency virus. Protease inhibitors are strong inhibitors of CYP3A and P-glycoprotein. Many studies have concluded the reduced requirement of CNIs and mTOR inhibitors when used along with Ritonavir, Lopinavir, and Nelfinavir alone or in combination.[24] The half-life of Tacrolimus has been reported to be increased 10-fold.[65] A dual interaction was also reported when Tacrolimus increased the levels of protease inhibitors. Other drugs that form part of highly active antiretroviral therapy do not showcase significant interactions with immunosuppression in the post-liver transplant patient.

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Antivirals for Cytomegalovirus Infection

Valganciclovir and Ganciclovir are the most used medications for the prophylaxis or treatment of cytomegalovirus (CMV). Neither of them exhibits interactions with CNIs. However, leukopenia and neutropenia may be seen when combined with MMF and/or Azathioprine. In a resistant CMV infection, the newer agent, Foscarnet, is used. Due to the synergistic or additive effect on nephrotoxicity, its combination with CNIs is not recommended.[66]

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) irreversibly block gastric acid secretion by binding to and inhibiting the hydrogen-potassium ATPase pump on the luminal surface of the parietal cell membrane. A study found that a comedication of pantoprazole with MMF significantly influenced the latter's drug exposure and immunosuppressive potency. The PPI-induced reduction of a mycophenolic fraction in plasma depends on the aqueous solubility of MMF, which shows greater solubility at pH < 5 and low solubility at pH > 6. The mofetil component of MMF is separated from the mycophenolic part in a pH-dependent fashion. In the presence of PPI and gastric pH > 4.5, there occurs reduced elution and hydrolysis of MMF, leading to lower levels of MPA.[67] A report demonstrated an interaction between Tacrolimus and Omeprazole, Esomeprazole but not Lansoprazole in an 18-yr-old female kidney transplant recipient who was a CYP 2C19 extensive metabolizer. Transplant physicians prescribing PPIs for the intermediate and long term in patients on Tacrolimus could consider monitoring immunosuppressant levels before initiating or switching PPIs.[68] A recent study showed that oral coadministration of Pantoprazole was safe in liver transplant recipients on tacrolimus, everolimus, or sirolimus, making it the PPI of choice as per the evidence-based use.[69] Among PPIs, only Rabeprazole is non-enzymatically converted into a thioether with the contribution from CYP2C19 and CYP3A4 with lower hepatic metabolism and has no significant drug–drug interactions with immunosuppressants.

Complementary and Alternative Medicines

Complementary and alternative medicines (CAMs) include supposed medicinal products which contain herbs, vitamins, minerals, pro and prebiotics, nutritional supplements, homeopathic remedies, and classical or proprietary traditional medicines, which include Ayurvedic, traditional Chinese, or Siddha and Unani medicines. The use of CAMs among the general and patient population is on the rise in India and other parts of the world due to the prolific but unscientific promotion of herbal and dietary supplements for chronic and lifestyle

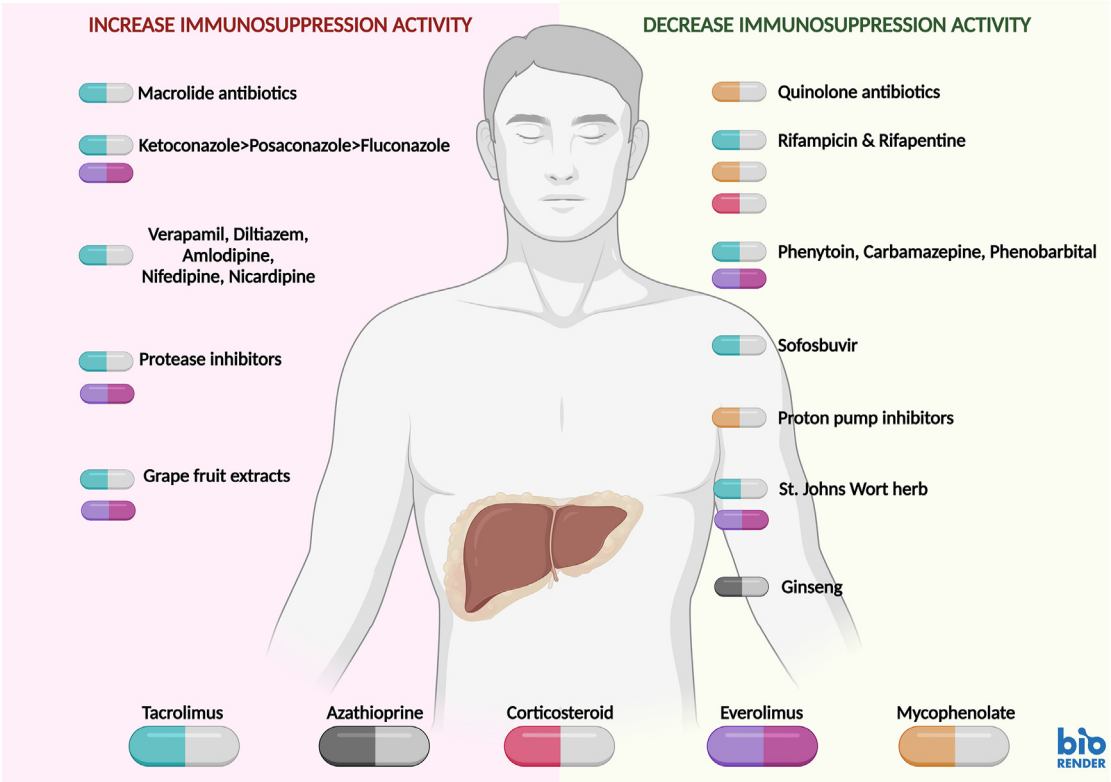

Figure 2 The infographic summary of interactions between various groups of medications with pertinently used immunosuppression agents in liver transplant recipients.

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illnesses.[70] It is imperative that treating physicians be aware of drug interactions and always ask what CAM products their patients are taking along with conventional medications. Panax Ginseng, or Asian Ginseng, is a commonly used herb that interacts with AZA and reduces its levels. Probiotic formulations containing *Lactobacillus acidophilus* may increase the risk of infections in patients with immunosuppression. St. John's Wort can reduce drug levels of mTOR inhibitors and CNIs by acting on their respective P-glycoprotein substrates. Nonetheless, the highest interaction of St. John's Wort is on a cyclosporine immunosuppressant, which reduces its trough levels quite extensively.[71] *Ginkgo biloba*, garlic, and fenugreek supplements can interact with antiplatelets and anticoagulants in the post-liver transplant period and increase bleeding susceptibility when used as comedications in those with metabolic syndrome. One of the commonest botanical interactions with immunosuppressants is grape-fruit juice and cyclosporine, followed by tacrolimus. Grapefruit, its extracts, or concentrates can interact with Everolimus, Sirolimus, and Tacrolimus via the inhibition of CYP3A4 and P-glycoprotein, leading to the potential increase in immunosuppression-related toxicity.[72] Recently, multiple reports and large multi-center series have shown that the herb *Tinospora cordifolia* or Giloy, used in traditional and proprietary Ayurvedic and Homeopathic practices, can induce autoimmune hepatitis in predisposed persons or cause a flare of quiescent autoimmune hepatitis in those with a previously stable disease. The mode of action suggested including immune modulation and polyclonal immunoglobulin secretion via a furano-diterpenoid phytochemical fraction in Giloy. These herbs with immune-modulating properties must be avoided in the post-liver transplant period, especially in those who were transplanted for autoimmune hepatitis.[73]

An infographic summarizing salient drug–drug interaction with immunosuppression medications in the liver transplant recipient is shown in Figure 2.

Liver transplant recipients are maintained on lifelong immunosuppression. Immunosuppressants are known to interact with a host of co-medications, and thorough the knowledge of drug–drug interactions, are pertinent to maintain stable immunosuppression for good graft function and avoiding drug toxicity. The main immunosuppressants include CNIs and mTOR inhibitors, and the drug–drug interactions mostly depend on the P450 (CYP) 3 A isoenzyme family member-related metabolism. Among antimicrobials, macrolides such as Azithromycin and Clarithromycin and quinolones such as Levofloxacin have significant drug interactions, especially related to QT prolongation and arrhythmias in the latter. The antitubercular drug, Rifampicin, reduced the enterohepatic circulation of MMF. Antifungals such as Fluconazole reduce, while Voriconazole and Posaconazole increase the levels of Tacrolimus. Levetiracetam is the preferred choice among antiepileptics as it lacks interactions with most immunosuppressants. Antihypertensives, Nifedipine and Amlodipine, have the potential to increase Tacrolimus levels. Among antivirals, protease inhibitors increase Tacrolimus levels, while direct-acting antivirals for HCV have no effect on immunosuppression. Anti-CMV agent, Foscarnet, can increase the risk of kidney toxicity when used with CNIs. Pantoprazole is the safest PPI in a post-liver transplant setting. CAMs must be avoided in the post-transplant period as they have no evidence of clinical benefits and could potentially cause liver injury or modulate immunosuppression levels for the worse.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Johns Shaji Mathew: conceptualization and writing (original draft and editing).

Cyriac Abby Philips: conceptualization, visualization, and writing (review and editing).

CONFLICTS OF INTEREST

The authors have no conflict of interests.

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