Original Article https://doi.org/10.22491/2357-9730.128108

Drug-drug interactions of immunosuppressants and other drugs in kidney post-transplant recipients

Mariel Umana-Rivas[1], Evelin Soares de Brito[2], Leticia da Silva Soares[1,2], Geraldo Rubens Ramos de Freitas[3], Pamela Alejandra Saavedra[4], Gustavo Queiroz Arimatea[3], Priscila Dias Gonçalves[3], Dayani Galato[1]

ABSTRACT

Introduction: Immunosuppressants (ISS) are the most crucial tools used in the therapeutic regimens of transplant recipients. Nevertheless, these drugs are not the only ones adopted by patients; therefore, knowing the possible drug-drug interactions (DDIs) between immunosuppressants and other drugs commonly used in kidney transplant recipients is essential to ensure the effectiveness and safety of treatments. In this way, the objective is analyzing the DDIs between the immunosuppressants and other commonly used medications on kidney transplant adult recipients with active medical records undergoing post-transplant follow-up for 4.4 years (mean).

Methods: First, we performed a cross-sectional study based on patients' records, in which the patient's profile and drugs used were examined, and after we analyzed DDIs by the Micromedex Drug Interactions® database.

Results: We analyzed 176 patients with a mean age of 47.6(± 12.5); most were male (67.7%), and the majority received a kidney from a deceased donor (81.4%). Patients were exposed to 15.0 (± 5.4) different medicines after the transplantation, and 7.4 (± 4.0) of these medicines were simultaneous. After analyzing the DDIs according to the severity of interaction, documentation quality interaction effect, clinical management and probable interaction mechanism, the most frequent interaction was with tacrolimus, classified as moderate, and the 3 major causes of interaction occurred with azathioprine according to the Micromedex database. The primary medicines involved with immunosuppressant interactions were proton pump inhibitors, ranitidine, domperidone, amlodipine, enalapril, allopurinol, cyclobenzaprine, amitriptyline, fluoxetine, and ciprofloxacin. These DDIs' effects were related to, mainly, increase their immunosuppressant activity.

Conclusion: Although the immunosuppressants analyzed lacked many clinical DDIs significance with other medicines, the healthcare team needs to monitor their DDIs' effects to prevent and minimize side effects in transplanted recipients.

Keywords: *Kidney transplantation; Drug interactions; Immunosuppressive agents; Renal insufficiency chronic; Nephrology*

Clin Biomed Res. 2023;43(2):116-135

1 Programa de Pós-Graduação em Ciências e Tecnologias em Saúde, Universidade de Brasília. Brasília, DF, Brasil.

2 Secretaria de Estado de Saúde do Distrito Federal. Brasília, DF, Brasil.

3 Hospital Universitário de Brasília. Brasília, DF, Brasil.

4 Conselho Federal de Farmácia. Brasília, DF, Brasil.

Corresponding author:
Dayani Galato
dayani.galato@gmail.com
Programa de Pós-Graduação em Ciências e Tecnologias em Saúde, Universidade de Brasília
Campus Universitário – Centro Metropolitano, Ceilândia Sul
72220-275, Brasília, DF, Brasil.

INTRODUCTION

Organ transplantation has been rising since the renowned Herrick brothers' transplant in 1954[1]. Since the first medicine many new treatments and improvements have led to a better recovery, organ acceptance, fewer rejections, and a better quality of life[1].

Brazil has its own national organ transplantation program, part of the Brazilian Public Unified Health System that offers free universal coverage, responsible for over 95% of the transplantations made in the country. Brazil has the most extensive worldwide public system in kidney transplantation, with 58,293 kidney transplants performed between 2011 and 2021[2,3].

Immunosuppressants are the cornerstone drugs for transplant recipients, used not just to prevent acute organ rejection, but also to treat other diseases such as

cancer and autoimmune diseases. Understanding the T cell's three signal model is essential to comprehending immunosuppressor's action mechanisms[4,5]. Alloimmune response initiates with an antigen-presenting cell (APC) presenting a donor antigen triggering T cell receptors (TCR/CD3) of naïve and memory T cells (signal 1) and a co-stimulated APC's CD80 (B7-1), CD86 (B7-2) or CD80/86 (B7) complexes engaging CD28 on T cells (signal 2). These first two signals' completion activates three transduction pathways (the calcium-calcineurin pathway, the RAS- mitogen-activated protein MAP kinase pathway, and the nuclear factor-κ*B* pathway), resulting in the expression of different molecules, such as interleukin-2 (IL-2), CD154, and CD25. IL-2 and IL-15 stimulate T cells receptors (signal 3), unchaining the mammalian target of rapamycin (mTOR) pathway, which triggers cell proliferation, and after nucleotide synthesis, T cells shift into effector phenotype[4,6,7].

Among drugs used in graft maintenance, there are calcineurin inhibitors, mTOR inhibitors, antimetabolic agents, nucleotide synthesis inhibitors, and glucocorticoids. Calcineurin inhibitors (tacrolimus and cyclosporine) inhibit calcineurin, not allowing IL-2 transcription, suppressing T cell and T cell-dependent B cell activation. Mycophenolate sodium (enteric-coated mycophenolate) inhibits guanosine monophosphate nucleotides and blocks purine synthesis, preventing the proliferation of T and B cells. Azathioprine is a nucleotide synthesis (DNA, RNA) and protein synthesis inhibitor. Glucocorticoids hinder several cytokine encoding genes, particularly IL-2[4,5].

Diabetes, hypertension, and dyslipidemia often co-occurs in chronic kidney disease patients and persist after kidney transplantation. With the multidrug immunosuppression strategy, knowing possible drug-drug interactions (DDIs) between the immunosuppressants and drugs used is crucial to treating comorbidities in the post-transplant follow-up period. The most common chronic diseases that lead to kidney transplantation can also be developed through the continuous use of immunosuppressants, are hypertension, diabetes mellitus, and dyslipidemia. Managing these chronic diseases and the immunosuppression in the clinical environment may become challenging due to the number of medicines used simultaneously. Nonetheless, DDIs analysis is not always a priority of the healthcare team. The long-term effects of immunosuppressants and their interaction with other commonly used drugs must likewise be considered in calculating the ideal immunosuppressant dose to prevent graft rejection while avoiding drug-specific complications and the risk of developing opportunistic infections or neoplasm occurrence[7-10].

This article reviews the DDIs between the most taken immunosuppressants and other commonly used medicines in the kidney transplant recipients from patients' records at the Brazilian Transplant Center, Brasília-DF, Brazil.

METHODS

This observational and cross-sectional study recruited patients from the outpatient clinic of a Brazilian Transplant Center located in Brasília, the capital of Brazil, connected to Brasília's University Hospital (HUB) and licensed for kidney and corneal transplants. We collected the epidemiological data in 2019 for all patients with active medical records in December of 2018, excluding those who died, were transferred to other care teams, were transplanted by other teams, pediatric patients and patients without physical records.

We performed data extraction from patients' records and analyzed drug-drug interactions (DDIs) from the IBM Micromedex Drug Interaction® database[11] and this project was approved by the Ethical Committee (CAEE 02637918.0.0000.8093).

Demographic data evaluated were age, gender, underlying renal disease, comorbidities, the time of follow-up, and type of donor. Data on the medicines used in ambulatorial care was also gathered. We investigated all medicines prescribed in the patients' records and used the Anatomical Therapeutic Chemical classification with Defined Daily Doses (ATC/DDD) index for the anatomic, chemical, and therapeutic drug classification[12].

We also analyzed each patient's medication list in the IBM Micromedex Drug Int® database for harmful interactions. The analyzed DDIs data were collected and organized in the severity of the interaction, documentation quality, interaction effect, clinical management (if the drug needs to be used simultaneously), and probable interaction mechanism.

The IBM Micromedex Drug Int® database classifies the DDI severity into five categories: contraindicated, major, moderate, mild, and unknown. Contraindicated drugs cannot be used concomitantly. Major DDI classification could represent life risk or may require medical intervention to diminish or avoid serious adverse effects, or both. Moderate interaction includes a possible exacerbation of the patient's base disease, a requirement of alteration (dosage)/change in their current medication, or both. Mild DDI classification may result in limited clinical effects that generally do not require changing the actual treatment.

The documentation quality was classified as excellent, good, poor, and unknown. Excellent documentation has controlled studies that clearly established the interaction's existence. Good documentation suggests that the interaction exists but lacks controlled studies to support this interaction. Poor documentation explains that the information available is unsatisfactory, though pharmacologic considerations lead the clinicians to suspect a possible interaction or that the information given is suitable for a similar drug. Finally, unknown means a lack of both the severity and documentation on the nature of the interaction and documents supporting the said interaction[11].

We organized the data in an Excel database and used descriptive analysis to present the results. The quantitative variables were presented as mean, median, and standard deviation and the qualitative variables were shown in percentage.

RESULTS

We analyzed 167 from 253 patients who received a renal transplant in the Brazilian Transplant Center at the HUB (Brasília University Hospital) and had active medical records in December of 2018, exclusion criteria can be consulted on methods.

In this health care unit, most patients were men (67.7%) and received the organ from deceased donors (81.4%). The total analyzed patients had a mean age of 47.6 (± 12.5) and a median age of 48 years.

The most common causes of chronic kidney disease (CKD) were chronic diseases such as hypertension (13.2%) and diabetes (10.2%), though often, the CKD cause is undetermined (34.7%). The patients included in the study were undergoing post-transplant follow-up for 4.4 (± 2.7) years (Table 1). The most common health problems identified in our research before and after transplantation were hypertension and diabetes mellitus (Table 1).

The most common classes of pharmaceuticals are presented in Figure 1 and detailed in Table 2. Clinicians prescribed seven different immunosuppressants and 265 other drugs in this healthcare unit, and patients were exposed to 15.0 (± 5.4) different medicine at home during this period after the transplantation and had a mean of 7.4 (± 4.0) simultaneously taken medicines.

The most used calcineurin inhibitor was tacrolimus (97%). Despite the lower use of cyclosporine in this center, some medical interactions involving this immunosuppressant were also found (Figure 2).

Among these drugs, thirty-four ferent possible drug-drug interactions (DDIs) between immunosuppressants and other drugs were identified, and only one was classified as contraindicated (Table 3). Seventy-five DDIs between non-immunosuppressive drugs were also found but were not included in this study. Among the immunosuppressants, most possible DDIs were related to tacrolimus and azathioprine. These DDIs commonly decrease the drug's effectiveness or safety by reducing their action or potentiating adverse effects, respectively. The other pharmacological classes involved with DDIs were quite diverse, including antimicrobials, anti-ulcers, antihypertensives, and central action drugs. Most described DDIs management was dose reduction or immunosuppressant dose monitoring.

Table 1: Renal Transplant Patient´s clinical profile from the Brazilian Transplant Center at the HUB (Brasilia University Hospital), Brazil, 2018.

Demographic data	**n (%)**
Gender (n = 167)	
- Male	113 (67.7)
- Female	54 (32.3)
Age * (n = 159)	
- Until 48 years	82 (49.1)
- More than 48 years	77 (46.1)
Base disease (n = 167)	
- Chronic Kidney Disease (undetermined)	58 (34.7)
- Diabetes Mellitus	17 (10.2)
- Hypertension	22 (13.2)
- Primary renal diseases**	25 (15.0)
Time post-transplantation* (n = 163)	
- Until seven years	74 (46.6)
- More than seven years	87 (53.4)
Time in dialysis before transplantation (n = 101)	
- Until five years	84 (83.2)
- More than five years	17 (16.8)

Continua...

Table 1: Continuação.

Demographic data	n (%)
Type of donor (n = 167)	
- Deceased donors	136 (81.4)
- Living donors	31 (18.6)

*Calculations made with the median.
** Primary diseases (glomerulopathies, nephrosclerosis, polycystic kidneys, and other non-specified).
Source adapted: Brito[13].

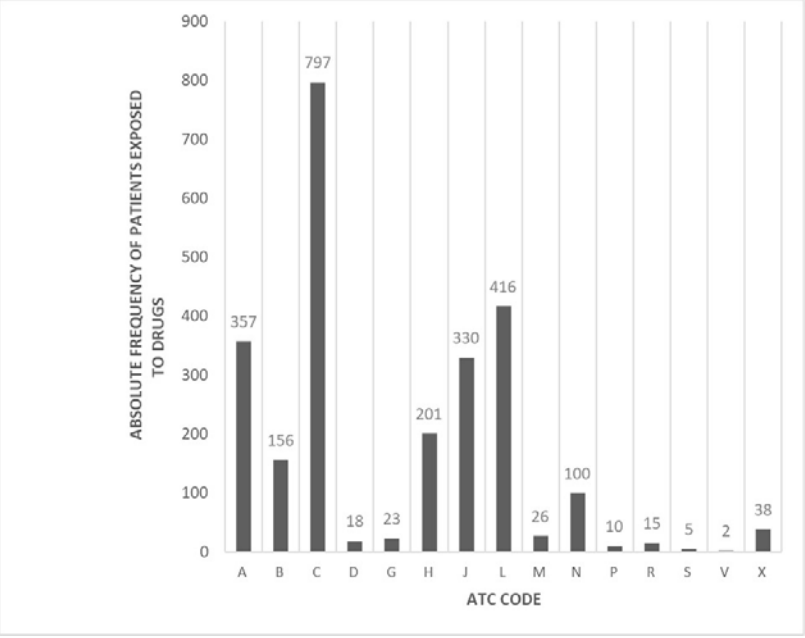

Figure 1: Drugs used* by transplant patients according to the leading anatomical group of the Anatomical, Therapeutic, and Chemical Classification (ATC), 2018 (167 patients).

*At least one prescription.
A: Alimentary tract and metabolism; B: Blood and blood-forming organs; C: Cardiovascular system; D: Dermatological; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infective for systemic use; L: Antineoplastic and immunomodulating agents; M: Musculo-skeletal system; N: Nervous system; P – Antiparasitic products, insecticides, and repellents; R: Respiratory system; S: Sensory organs; V: Various; X: Unclassified, such as phytotherapies.
Source: Brito[13].

Table 2: Frequency of the main non-immunosuppressive drugs used, by the anatomical, therapeutic chemical (ATC) classification, in renal transplant patients in the university hospital in Brasília (HUB), 2018.

ATC Drug Classification	Frequency n (%)
A: Alimentary tract and metabolism (n = 357)	
Omeprazole	161 (96.4)
Metformin	32 (19.2)
Insulin (NPH)	29 (17.4)
Others*	135
B: Blood and blood-forming organs (n = 156)	
Salicylic Acid	45 (26.9)
Erythropoietin	30 (18.0)
Ferrous sulfate	28 (16.8)
Others*	53

Continua...

Table 2: Continuação.

ATC Drug Classification	Frequency n (%)
C: Cardiovascular system (n = 797)	
Amlodipine	133 (79.6)
Atenolol	99 (59.3)
Furosemide	92 (55.1)
Simvastatin	82 (49.1)
Clonidine	68 (40.7)
Enalapril	61 (36.5)
Losartan	46 (27.5)
Hydrochlorothiazide	40 (24.0)
Others*	176
D: Dermatological (n = 18)	
Nystatin	9 (5.4)
Ketoconazole	4 (2.4)
Others*	5
G: Genito urinary system and sex hormones (n = 23)	
Oxybutynin	6 (3.6)
Sildenafil	2 (1.2)
Tadalafil	2 (1.2)
Progesterone	2 (1.2)
Others*	11
H: Systemic hormonal preparations excluding sex hormones and insulin (n = 201)	
Prednisone	164 (98.2)
Levothyroxine sodium	21 (12.6)
Cinacalcet	11 (6.6)
Others*	5
J: Anti-infectives for systemic use (n = 330)	
Trimethoprim sulfamethoxazole	130 (77.8)
Ciprofloxacin	37 (22.1)
Ganciclovir	22 (13.2)
Others*	141
L: Immunosuppressants	
Tacrolimus	162 (97.0)
Sodium mycophenolate	122 (73.0)
Sirolimus	54 (32.3)
Everolimus	53 (31.7)
Azathioprine	18 (10.8)
Cyclosporine	6 (3.6)
Mycophenolate mofetil	1 (0.6)
M: Musculoskeletal system (n = 26)	
Allopurinol	14 (8.4)
Cyclobenzaprine	3 (1.8)
Others*	9
N: Nervous system (n = 100)	
Amitriptyline	14 (8.4)
Fluoxetine	11 (6.6)
Clonazepam	11 (6.6)
Zolpidem	8 (4.8)
Others*	66

Continua...

Table 2: Continuação.

ATC Drug Classification	Frequency n (%)
P: Antiparasitic products (n = 11)	
Albendazole	4 (2.4)
Others*	7
R: Respiratory system (n = 15)	
Loratadine	4 (2.4)
Budesonide	2 (1.2)
Mupirocin	2 (1.2)
Others*	7
S: Sense organs	
Chloramphenicol ophthalmologic solution	2 (1.2)
Others*	3
V: Various (n = 2)	
Sevelamer**	1 (0.6)
Pancreozymin	1 (0.6)

* It is not possible to calculate the percentage; ** Used only on immediate renal transplantation.
Source: adapted Brito[13].

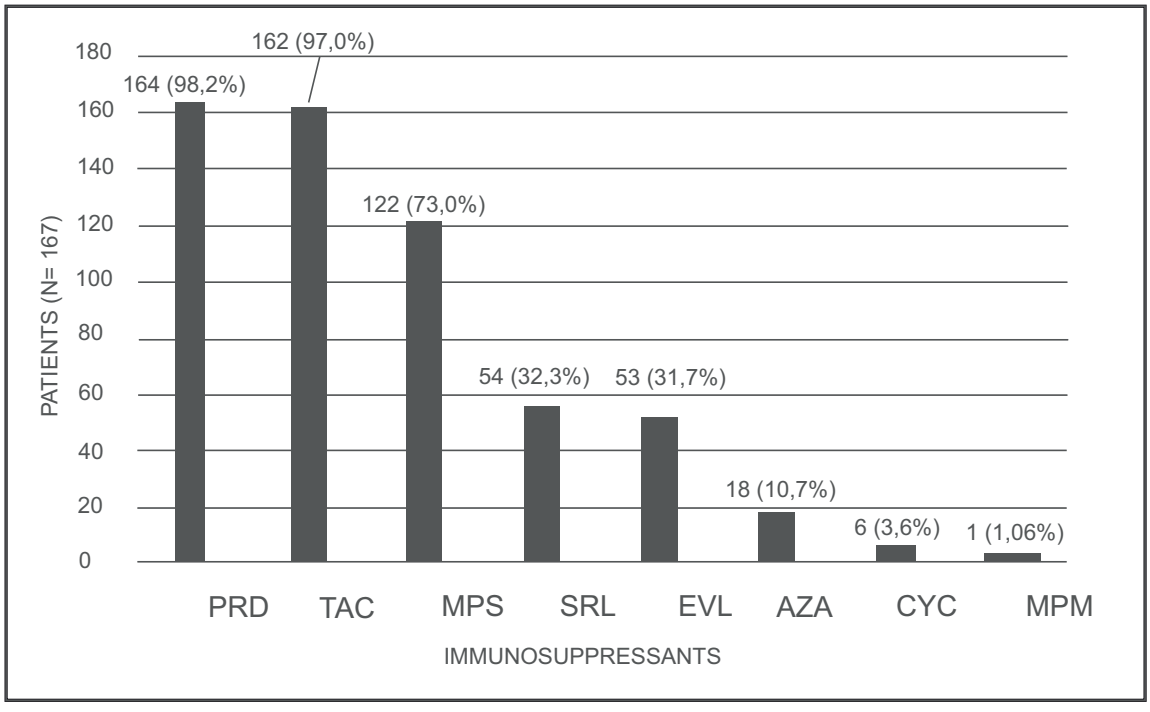

Figure 2: Frequency of patients in ambulatory service exposed to immunosuppressants* in a Brazilian University Hospital, 2018 (n = 167 patients).

*Register at least one prescription.PRD: Prednisone; TAC: Tacrolimus; MPS: Sodium mycophenolate; SRL: Sirolimus; AZA: Azathioprine; CYC: Cyclosporine; MPM: Mycophenolate mofetil.Source: Brito[13].

Table 3: Immunosuppressants and their drug-drug interactions (DDIs) with the commonly used non-immunosuppressive drugs in post-kidney transplant patients based on IBM Micromedex® database.

IMMUNOSUPPRESSANT	CYC	AZT	EVR	MIC	PRD	SRL	TAC
Alimentary Tract and Metabolism							
Omeprazole	▲			▲			▲
Esomeprazole	▲			▲			▲
Pantoprazole	▲			▲			▲
Ranitidine hydrochloride							▲
Cimetidine	■					■	
Domperidone	▲						▲
Blood and Blood-forming organs							
Salicylic acid	▲						▲
Cardiovascular System							
Amlodipine	▲						▲
Enalapril	■	▲	▲			▲	
Hydrochlorothiazide					■		
Simvastatin	x						
Dermatological							
Ketoconazole	■				■		▲
Musculoskeletal System							
Allopurinol	■	▲					
Cyclobenzaprine							▲
Nervous System							
Amitriptyline hydrochloride							▲
Fluoxetine							▲
Anti-infectives for systemic use							
Ciprofloxacin	■			▲	▲		
TMP SMX		▲					
Ganciclovir				■			■

▲: Major DDIs; ■: Moderate DDIs; **x**: Contraindicated DDIs.

AZT: Azathioprine; EVR: Everolimus; MIC: Sodium mycophenolate; PRD: Prednisolone; SRL: Sirolimus; TAC: Tacrolimus; TMP SMX: Trimethoprim-sulfamethoxazole.

The three major DDIs occurred with azathioprine. The first DDI with allopurinol causes toxicity and requires reducing the dose to ¼ of azathioprine. The second DDI with enalapril maleate induces myelosuppression and requires close monitoring if coadministration is needed. Finally, the last DDI with sulfamethoxazole/trimethoprim augments the risk of bone marrow suppression, especially in renal transplants (Supplement 1).

Tacrolimus had twelve DDIs with other drugs found (Table 3), eleven major and one moderate. It interacted with proton-pump inhibitors, such as amlodipine, ranitidine hydrochloride, and ketoconazole, resulting in increased tacrolimus exposure (Supplement 1).

Both cyclobenzaprine and domperidone showed a high risk of QT-interval prolongation when combined with tacrolimus. Prednisone may decrease tacrolimus levels if used together and, thus, increase the risk of organ rejection. As for the documentation quality, it was considered regular in most situations (61.5%).

DISCUSSION

Tacrolimus is the most prescribed immunosuppressive drug in combination with sirolimus in the transplant service where this study was conducted. In Vitko et al.'s[14] multicenter study, the tacrolimus-sirolimus combination regimen showed a significantly lower incidence of biopsy-proven acute rejection compared with other therapeutic regimens, such as tacrolimus-mycophenolate or cyclosporin-sirolimus. Nonetheless, the tacrolimus-sirolimus regimen also showed elevated total serum cholesterol levels; this elevation can be attributable solely to sirolimus, and if statins treatment does not normalize serum cholesterol levels, reducing sirolimus dose without compromising the immunosuppressive efficacy might be a possible solution[14].

Patients who undergo kidney transplantation surgery have at least a previously developed chronic kidney disease (CKD), generally accompanied by other comorbidities such as hypertension or diabetes, or sometimes both. These underlining conditions result in a considerable quantity of drugs per patient, which, in most cases, is the only way to maintain their comorbidities stabilized. Noticeably, when analyzing immunosuppressants' interactions with the most common drugs used in kidney transplanted patients, the immunosuppressants from the antimetabolite agents and the calcineurin inhibitors families showed the most drug-drug interactions (DDIs)[15-17].

The immunosuppressants are used in higher doses at the beginning of the post-transplant until the highest risk of graft rejection surpasses. Once this period passes, the dosage of these drugs will drop until reaching a maintenance level that would probably last their entire life. In most cases, monitoring of pharmacological interactions is essential as DDIs are not always dose-dependent and have the possibility of occurring when a lower dose is administered[18].

Our patients' profiles included gender, age, base disease, the time within the renal service, and type of donor. Similar to Ribeiro et al.[19] study in which 66.7% of the recipients were male, the majority of patients were male (67%). This prevalence toward male recipients is expected as one of the most important causes of renal transplant is CKD, which is more common in males than females. Luvisotto, Carvalho, and Galdeano[20] considered that all transplant recipients' base disease was CKD and that 49% of the patients were diagnosed with hypertension and 20% with diabetes was due to this base disease.

Polypharmacy in transplanted kidney recipients is not just correlated to immunosuppressive therapy but also with other drugs used for health problems such as diabetes mellitus, hypertension, and primary kidney diseases and for the prophylaxis protocols such as the use of sulfamethoxazole-trimethoprim and omeprazole. Importantly, drugs such as nystatin, albendazole, and ivermectin are in the list of medicines used for prophylaxis in the immediate post-transplant process, which is why they were not included in the most used drugs' list in the ambulatory service[21].

One of the most adverse DDIs with azathioprine is with xanthine oxidase activity inhibitors (e.g., allopurinol), as xanthine oxidase takes part in azathioprine metabolism. This combination might cause severe leukopenia; hence it should be avoided. If the combination must be used, careful monitoring of the white blood cell count becomes necessary[22].

Studies revealed that some drugs could increase blood levels when combined with immunosuppressants, such as calcineurin inhibitors, tacrolimus, and cyclosporine. We found in the Micromedex database that the recommendation for calcium channel blockers was to monitor doses carefully for higher concentrations or toxicity of the immunosuppressant. A single-dose study from China evaluated the CYP3A45*3 allele's effects on the tacrolimus and amlodipine pharmacokinetics and established significant DDIs involving the CYP3A45*3 between these two drugs[23].

According to our database research, the interaction between allopurinol and azathioprine could be monitored by reducing the immunosuppressant dose. Even though research evidence recommends that this combination be avoided as the outcomes from this interaction are not secure[24].

Another important interaction unidentified by our database is between ganciclovir and mycophenolate, used for treating Cytomegalovirus. Although the concentration in which these two drugs are used together has not shown significance, it is essential to evaluate other potential adverse effects, especially their gastrointestinal effects[25].

Another unidentified drug-drug interaction in our Micromedex database study was the interaction between isoniazid and immunosuppressants used for tuberculosis treatment, one of the most important opportunistic infections in transplant recipients. Explained in several studies as possible hepatotoxicity, this case type of interaction is moderate and causes elevated levels of immunosuppressants, needing laboratory monitoring for dose adjustment. The absence of this interaction in our sample study could be explained by a low prevalence of tuberculosis in the local healthcare service and the triage treatment protocol for all patients on the transplants list[26].

In renal transplanted patients, the number of medications and their dose is high in the first months after surgery to prevent graft rejection. Immunosuppressants are the main drugs part of the transplanted patients' primary treatment schedule that interact with many drugs also used in these patients' treatment, such as antihypertensives, anti-acids, anti-inflammatory, and other drugs.

Immunosuppressive therapy maintenance is the most critical step in the transplant puzzle for successful organ transplantation. Consequently, knowing the possible interactions of immunosuppressive drugs with other drugs used by the recipient aids in providing the most suitable drug combination to keep the patients' new organ functionating while decreasing the drugs' side-effects, thus providing them a better life quality. The immunosuppression in organ transplantation prevents graft rejection and helps minimize undesired side effects such as infection, malignancy, and drug toxicity. It is not uncommon for kidney recipients to take two immunosuppressants concurrently in their daily routine for extended periods; some must keep taking at least two immunosuppressants for their entire lifetime. When prescribing two immunosuppressants, knowing the best combinations and avoiding the least compatible ones is vital for clinicians. For this, it is essential to combine two different classes of immunosuppressants and a glucocorticoid, most frequently prednisone.

DDIs' clinical impact involves both pharmacokinetics and pharmacodynamic effects reflected in the clinical observation and changes in the medications' serum concentrations. In this context, DDIs can favor clinical treatment, and by knowing and learning their effects, the healthcare team can properly establish appropriate drug management[27].

Our study has some limitations. As an observational study, it might be missing clinical experience data from the transplant service and their most common DDIs involving immunosuppressants, as well as missing DDIs that went undetected in the IBM Micromedex® Drug Int database. Furthermore, it is a single institution study with a small sample size that involved only drugs that outpatients use.

It is worth mentioning that this is preliminary work and must be updated in short periods to ensure that it is updated with the current drug combinations protocol used in the different care units.

It is fundamental for all health providers to understand the drug-drug interaction (DDIs) of the drugs they prescribe their patients. This understanding and access to different tools (e.g., IBM Micromedex® Drug Int) enable health providers to determine the most suitable for their patient's specific profile from the possible drug combinations available, thus helping prevent or minimize adverse effects.

Our work analyzed the Brazilian Transplant Center at the HUB (Brasilia University Hospital) ambulatory drug use list determining the most critical medical interactions between immunosuppressants and other drugs used by the renal transplanted outpatients.

Acknowledgments

Transplant Service of the University Hospital of Brasília (HUB) and the financial support by Coordination for the Improvement of Higher Education Personnel (CAPES).

REFERENCES

1. Doyle AM, Lechler RI, Turka LA. Organ transplantation: halfway through the first century. *J Am Soc Nephrol*. 2004;15(12):2965-71.
2. Medina-Pestana JO, Galante NZ, Tedesco-Silva H Jr, Harada KM, Garcia VD, Abbud-Filho M, et al. Kidney transplantation in Brazil and its geographic disparity. *J Bras Nefrol*. 2011;33(4):472-84.
3. Associação Brasileira de Transplante de Órgãos. *Registro brasileiro de transplantes*. Dados númericos da doação de órgãos e transplantes realizados por estado e instituição no período: janeiro/junho – 2021. São Paulo: ABTÓ; 2021.
4. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med*. 2004;351(26):2715-29.
5. Belmont HM. *Pharmacology and side effects of azathioprine when used in rheumatic diseases* [Internet]. Waltham: UpToDate; 2014 [cited 2023 July 13]. Available from: http://www.uptodate.com/contents/pharmacology-and-side-effects-of-azathioprine-when-used-in-rheumatic-diseases#H6
6. Goldfarb DA. Immunosuppressive drugs for kidney transplantation. *J Urol*. 2005;173(6):2105.
7. Gaston RS. Maintenance immunosuppression in the renal transplant recipient: an overview. *Am J Kidney Dis*. 2001;38(6 Suppl 6):S25-35.
8. Glicklich D, Lamba R, Pawar R. Hypertension in the kidney transplant recipient: overview of pathogenesis, clinical assessment, and treatment. *Cardiol Rev*. 2017;25(3):102-9.

9. Vanhove T, Remijsen Q, Kuypers D, Gillard P. Drug–drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus. *Transplant Rev (Orlando)*. 2017;31(2):69-77.

10. Warden BA, Duell PB. Management of dyslipidemia in adult solid organ transplant recipients. *J Clin Lipidol*. 2019;13(2):231-45.

11. *Merative Micromedex®*: web applications access [Internet]. New York: IBM; [cited 2021 July 27]. Available from: https://www.micromedexsolutions.com/home/dispatch/ssl/true

12. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD Index* [Internet]. Geneva: WHO; [cited 2021 July 27]. Available from: https://www.whocc.no/atc_ddd_index/.

13. Brito ES. *Perfil do uso de medicamentos em pacientes transplantados renais de um hospital universitário* [master's thesis]. Brasília (DF): Universidade de Brasília; 2020.

14. Vitko S, Wlodarczyk Z, Kyllönen L, Czajkowski Z, Margreiter R, Backman L, et al. Tacrolimus combined with two different dosages of sirolimus in kidney transplantation: results of a multicenter study. *Am J Transplantation*. 2006;6(3):531-8.

15. Allison TL. Immunosuppressive therapy in transplantation. *Nurs Clin North Am*. 2016;51(1):107-20.

16. Garcia GG, Harden P, Chapman J. O papel global do transplante renal. *J Bras Nefrol*. 2012;34(1):1-7.

17. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde. Departamento de Gestão e Incorporação de Tecnologias e Inovação em Saúde. Coordenação-Geral de Gestão de Tecnologias em Saúde. Coordenação de Gestão de Protocolos Clínicos e Diretrizes Terapêuticas. *Protocolo clínico e diretrizes terapêuticas da imunossupressão em transplante renal*. Brasília (DF): Conitec; 2020.

18. Bressan AL, Silva RS, Fontenelle E, Gripp AC. Imunossupressores na dermatologia. *An Bras Dermatol*. 2010;85(1):9-22.

19. Ribeiro MVG, Zanesco C, Berlezi GF, Silva DTR. Perfil e desfecho clínico de pacientes transplantados renais em um serviço especializado: desfechos de um projeto de extensão. *Cid Açao*. 2018;2(2):20-31.

20. Luvisotto MM, Carvalho R, Galdeano LE. Transplante renal: diagnósticos e intervenções de enfermagem de pacientes no pós-operatório imediato. *Einstein (Sao Paulo)*. 2007;5(2):117-22.

21. Papotti B, Marchi C, Adorni MP, Potì F. Drug-drug interactions in polypharmacy patients: the impact of renal impairment. *Curr Res Pharmacol Drug Discov*. 2021;2:100020.

22. Vella J, Brennan DC. *Kidney transplantation in adults*: induction immunosuppressive therapy [Internet]. Waltham: UpToDate; 2020 [cited 2023 July 13]. Available from: https://www.uptodate.com/contents/kidney-transplantation-in-adults-induction-immunosuppressive-therapy

23. Zuo XC, Zhou YN, Zhang BK, Yang GP, Cheng ZN, Yuan H, et al. Effect of CYP3A5*3 polymorphism on pharmacokinetic drug interaction between tacrolimus and amlodipine. *Drug Metab Pharmacokinet*. 2013;28(5):398-405.

24. Cummins D, Sekar M, Halil O, Banner N. Myelosuppression associated with azathioprine-allopurinol interaction after heart and lung transplantation. *Transplantation*. 1996;61(11):1661-2.

25. Meesing A, Razonable RR. New developments in the management of cytomegalovirus infection after transplantation. *Drugs*. 2018;78(11):1085-103.

26. *Lexicomp® Drug Interactions* [Internet]. Waltham: UpToDate; [cited 2022 Mar 4]. Available from: https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist

27. Caterina P, Di Paolo A, Giofrè C, Caglioti C, Leuzi G, Siniscalchi A, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J Res Med Sci*. 2013;18(7):601-10.

Received: Oct 26, 2022
Accepted: Apr 24, 2023

SUPPLEMENT 1

Immunosuppressants and their drug interactions with the most common drugs used in the transplant center at the HUB (Brasilia University Hospital).

MEDICAL INTERACTIONS					
Contraindicated					
ISS	**OTHER DRUG**	**INTERACTION EFFECT**	**CLINICAL MANAGEMENT**	**PROBABLE MECHANISM**	**DOCUMENTATION**
Cyclosporine	Simvastatin	Concurrent use may result in an increased risk of myopathy or rhabdomyolysis.	Concomitant use may increase the risk of developing myopathy/ rhabdomyolysis and is contraindicated. Consider switching to a statin (Fluvastatin, pravastatin, rosuvastatin).	Inhibition of CYP3A4-mediated metabolism of simvastatin by cyclosporine; inhibition of OATP1B1-mediated simvastatin transport by cyclosporine.	

Major					
DRUG 1	**DRUG 2**	**INTERACTION EFFECT**	**CLINICAL MANAGEMENT**	**PROBABLE MECHANISM**	**DOCUMENTATION**
Azathioprine	Allopurinol	Concurrent use may result in azathioprine toxicity (nausea, vomiting, leukopenia, anemia).	If coadministration is required: reduce the dose of azathioprine to 1/3 to 1/4 of the usual dose. Monitor closely and adjust subsequent doses based on response to therapy and presence of toxicities.	Inhibition of xantine oxidase.	Excellent
Azathioprine	Enalapril maleate	Concurrent use may result in myelosuppression.	Avoid this combination. If these two drugs are administered concomitantly, monitor patients for myelosuppression (anemia, leukemia).	Unknown	Good

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Azathioprine	Sulfametoxazole/ Trimethoprim	Concurrent use may result in increased risk of bone marrow suppression.	May enhance bone marrow suppressing activity of one or both drugs and increased risk of leucopenia, especially in renal transplant patients.	Additive myelosuppressive effects.	Fair
Cyclosporine	Domperidone	Concurrent use may result in increased domperidone exposure and an increased risk of QT prolongation.	Use caution as this may result in increased plasma concentrations of domperidone and may increase risk of serious cardiac effects, including ventricular arrhythmias and sudden cardiac death.	Inhibition of CYP3A4-mediated domperidone metabolism.	Fair
Cyclosporine	Salicylic Acid	Concurrent use with nonsteroidal antiinflamatory agents may result in increased risk of cyclosporine nephrotoxicity.	Use caution when coadministering and closely monitor renal function.	Decreased synthesis of renal prostacyclin.	Excellent
Everolimus	Enalapril	Concurrent use of ACE inhibitors and mTOR inhibitors may result in increased risk of angioedema.	Consider avoiding this combination by using an angiotensin receptor blocker instead of an ACE inhibitor.	Unknown	Excellent

Continua...

SUPPLEMENT 1 :Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Everolimus	Ketoconazole	Concurrent use of Everolimus and Dual Strong CYP3A4 and P-glycoprotein inhibitors may result in increased everolimus.	Avoid coadministration in: patients with breast cancer, progressive neuroendocrine tumors of pancreatic origin, renal cell carcinoma, renal angiomyolipoma with tuberous sclerosis complex, or subependymal giant cell astrocytoma with TSC due to the potential for elevated everolimus plasma concentrations.	Inhibition of CYP3A4-mediated metabolism and P-glycoprotein efflux transport of everolimus.	Fair
Mycophenolate Sodium	Ciprofloxacin	May result in decreased mycophenolic acid plasma exposure.	May lead to decreased exposure to the active metabolite mycophenolic acid and decreased efficacy of mycophenolate mofetil. When coadministration is required, monitor patients for alterations in efficacy or mycophenolate mofetil-related adverse reactions. Obtaining MPA plasma levels before and after the initiation of discontinuation of concomitant medications may be necessary to ensure MPA levels remain stable.	Inhibition of enterohepatic recirculation of mycophenolic acid by ciprofloxacin	Excellent

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Mycophenolate Mofetil	Omeprazole, Esomeprazole, Pantoprazole	Concurrent use of MMS and proton pump inhibitors may result in reduced exposure to mycophenolic acid.	Monitor patients for alterations in efficacy when coadministration with a PPI is required. Obtaining MPA plasma levels before and after the initiation or discontinuation of concomitant medications may be necessary to ensure MPA levels remain stable.	Incomplete dissolution and decreased absorption of mycophenolate mofetil when the gastric pH is increased.	Excellent
Prednisolone	Ciprofloxacine	Concurrent use of selected corticosteroids and selected fluoroquinolones may result in an increased risk of tendon rupture.	Discontinue immediately if the patient experiences pain, swelling, inflammation, or rupture of a tendon.	Additive effect of risk for tendon rupture.	Excellent
Prednisolone	Salicylic Acid	Concurrent use of Corticosteroids and NSAIDS may result in increased risk of gastrointestinal ulcer or bleeding.	If coadministration is necessary, monitor for signs of bleeding.	Additive effects.	Fair
Sirolimus	Enalapril Maleate	Concurrent use of ACE inhibitors and mTOR inhibitors may result in increased risk of angioedema.	Consider avoiding this combination by using an angiotensin receptor blocker instead of an ACE inhibitor.	Unknown	Excellent
Sirolimus	Ketoconazole	Concurrent use may result in increased risk of sirolimus toxicity (anemia, leukopenia, thrombocytopenia, hypokalemia, diarrhea).	Coadministration of CYP3A4 and p-glycoprotein inhibitor is not recommended, consider alternative antifungal therapy.	Inhibition of cytochrome P4503A4 and p-glycoprotein-mediated sirolimus metabolism.	Excellent

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Tacrolimus	Amlodipine	Concurrent use of amlodipine and tacrolimus may result in increased tacrolimus exposure.	Monitor trough tacrolimus concentrations frequently after starting amlodipine therapy and adjust the tacrolimus dosage if appropriate. Also monitor the patient for signs of tacrolimus toxicity, including renal dysfunction, cholestasis and paresthesia.	Unknown	Fair
Tacrolimus	Amitriptiline hydrochloride	Concurrent use of tacrolimus and QT interval prolonging drugs may result in increased risk of QT-interval prolongation.	Concomitant use may increase the risk of serious cardiac toxicity, including torsade de pointes. If coadministered, monitor tacrolimus whole blood concentrations and for QT interval prolongation, and consider monitoring magnesium, potassium, and calcium blood levels.	Additive effects on QT interval.	Fair
Tacrolimus	Ciclobenzaprine Hydrochloride	Concurrent use tacrolimus and mild or moderate CYP3A inhibitors that prolong QT interval may result in increased tacrolimus trough concentrations and increased risk of QT-interval prolongation.	If coadministred, reduce tacrolimus dose, monitor tacrolimus blood levels and for QT prolongation, and consider monitoring magnesium, potassium, and calcium blood levels.	Inhibition of CYP3A-mediated tacrolimus metabolism and additive effects on QT interval.	Fair

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Tacrolimus	Domperidone	Concurrent use of Domperidone and Tacrolimus may result in increased risk of QT interval prolongation.	Use caution when coadministering domperidone and tacrolimus as it may increase the risk of serious cardiac effects, including ventricular arrhythmias and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, initiate domperidone at the lowest possible dose and titrate with caution.	Additive effects on the QT interval.	Fair
Tacrolimus	Fluoxetine Hydrochloride	Concurrent use of Fluoxetine and QT interval prolonging drugs may result in increased risk of QT-interval prolongation.	Avoid the concomitant use of fluoxetine with other drugs known to prolong the QT interval. If coadministration is necessary, consider a baseline ECG and on-treatment monitoring.	Additive QT-interval prolonging effects.	Fair

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Tacrolimus	Ketoconazole	Concurrent use of may result in increased tacrolimus concentrations and increased risk of QT-interval prolongation.	Coadministration of oral or IV tacrolimus with a strong CYP3A4 inhibitor, is not recommended without dose adjustments of tacrolimus and subsequent monitoring of tacrolimus blood levels and tacrolimus-associated adverse reactions. Coadministration may result additive effects on QT-interval prolongation and an increased risk of serious cardiovascular effects. If concomitant used is required, initiate oral or IV tacrolimus at lower dosage, closely monitor tacrolimus whole blood concentrations, observe for signs and symptoms of QT interval prolongation, and consider obtaining an ECG and monitoring magnesium, potassium, and calcium levels.	Inhibition of CYP3A4-mediated tacrolimus metabolism and additive effects on QT interval.	Good

Continua...

SUPPLEMENT 1: Continuação.

DRUG 1	DRUG 2	INTERACTION EFFECT	CLINICAL MANAGEMENT	PROBABLE MECHANISM	DOCUMENTATION
Tacrolimus	Esomeprazole Omeprazole	Concurrent use of Omeprazole and Tacrolimus may result in increased tacrolimus exposure.	It may be prudent to avoid coadministration. If omeprazole and tacrolimus are used together, monitor tacrolimus levels and make dosage adjustments as necessary, and monitor for tacrolimus toxicity.	Inhibition of CYP3A4-mediated tacrolimus metabolism.	Good
Tacrolimus	Ranitidine Hydrochloride	Concurrent use of Tacrolimus and mild/moderate CYP3A4 inhibitors may result in increased tacrolimus trough concentrations and increased risk of toxicity.	If coadministred, monitor tacrolimus whole blood trough concentrations and the risk of serious toxicity.	Inhibition of CYP3A4-mediated tacrolimus metabolism.	Fair
Tacrolimus	Salicylic Acid	Concurrent use may result in renal acute failure.	Concomitant administration should be avoided, particularly in patients with liver dysfunction. If use concurrently monitor serum creatinine and urine output.		Good

Moderate					
ISS	**OTHER DRUG**	**INTERACTION EFFECT**	**CLINICAL MANAGEMENT**	**PROBABLE MECHANISM**	**DOCUMENTATION**
Cyclosporine	Allopurinol	Concurrent use may result in increased cyclosporine levels.	Consider monitoring cyclosporine levels and adjusting the dosage if coadministration is required.	Unknown	Good
Cyclosporine	Cimetidine	Concurrent use may result in increased risk of cyclosporine toxicity.	Monitor patients for increased cyclosporine toxicity (renal dysfunction, neurotoxicity).	Unknown; competition between cimetidine and creatinine for renal tubular secretion.	Good

Continua...

SUPPLEMENT 1: Continuação.

Moderate					
ISS	**OTHER DRUG**	**INTERACTION EFFECT**	**CLINICAL MANAGEMENT**	**PROBABLE MECHANISM**	**DOCUMENTATION**
Cyclosporine	Ciprofloxacin	Concurrent use may result in increased cyclosporine blood levels, loss of cyclosporine therapeutic effect or transient elevations in serum creatinine.	When using in transplant patients for immunosuppression, monitor cyclosporine blood levels and monitor for signs of rejection.	Decreased cyclosporine metabolism; pharmacodynamic antagonism.	Excellent
Cyclosporine	Enalapril Maleate	Concurrent use may result in renal dysfunction.	Monitor renal function closely in patients taking enalapril and cyclosporine.	Not specified.	Fair
Cyclosporine	Ketoconazole	Concurrent use may result in an increased risk of cyclosporine toxicity.	This drug interaction may be used intentionally as a cost saving measure to reduce the effective dose of cyclosporine. If this interaction is nor desired, consider use of an alternate antimicrobial.	Altered cyclosporine absorption/metabolism; inhibition of cyclosporine hydroxylase in human liver microsomes	Excellent
Cyclosporine	Omeprazole	Concurrent use may result in altered cyclosporine concentrations.	Monitor circulating cyclosporine levels and adjust cyclosporine dosage as necessary.	Altered cyclosporine metabolism.	Fair
Sirolimus	Cimetidine	Concurrent use of Cimetidine and Sirolimus may result in an increased risk of sirolimus toxicity (anemia, leukopenia, thrombocytopenia, hypokalemia, fever, diarrhea).	Monitor sirolimus levels and adjust sirolimus dosage accordingly. Monitor the patient for sirolimus toxicity.	Inhibition of CYP-450 mediated sirolimus metabolism.	Fair
Prednisolone	Hidroclorotiazide	Concurrent use may result in Hypokalemia,	Potassium balance should be carefully monitored when corticosteroid therapy is initiated, discontinued, or altered in patients who receive chronic thiazide diuretics.	Additive kaluresis.	Fair

Continua...

SUPPLEMENT 1: Continuação.

Moderate					
ISS	**OTHER DRUG**	**INTERACTION EFFECT**	**CLINICAL MANAGEMENT**	**PROBABLE MECHANISM**	**DOCUMENTATION**
Prednisolone	Ketoconazole	Concurrent use may result in increased risk of corticosteroid side effects.	May require adjustment when ketoconazole is added or deleted from their drug regiments. Also monitor for adverse effects of prednisolone, including neuropsychiatric reactions, fluid and electrolyte disturbances, hypertension, and hyperglycemia.	Decreased prednisolone metabolism.	Fair
Tacrolimus	Ganciclovir	Concurrent use of ganciclovir and tacrolimus may result in an increased risk of nephrotoxicity.	Renal function tests should be given prior to and during concomitant ganciclovir/ valganciclovir and tacrolimus therapy. Avoiding high doses of tacrolimus may protect renal function.	Additive nephrotoxicity.	Fair

Source: IBM Micromedex – Drug Interactions®.