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ORIGINAL ARTICLE

Real clinical impact of drug–drug interactions of immunosuppressants in transplant patients

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Abstract

The main objective was to determine the prevalence of real drug–drug interactions (DDIs) of immunosuppressants in transplant patients. We conducted a prospective, observational 1-year study at a tertiary hospital, including all transplanted patients. We evaluated data from monitoring blood concentrations of immunosuppressive drugs and adverse drug events (ADEs) caused by DDIs. The DDIs were classified as C, D, or X according to their Lexi-Interact rating (C = monitor therapy, D = consider therapy modification, X = avoid combination). The clinical importance of real DDIs was expressed in terms of patient outcomes. The causality of DDIs was determined using Drug Interaction Probability Scale. The data were analyzed using Statistical Package for Social Sciences v. 25.0. A total of 309 transplant patients were included. Their mean age was 52.0 ± 14.7 years (18–79) and 69.9% were male. The prevalence of real DDIs was 21.7%. Immunosuppressive drugs administered with antifungal azoles and tacrolimus (TAC) with nifedipine have a great clinical impact. Real DDIs caused ADEs in 22 patients. The most common clinical outcome was nephrotoxicity (1.6%; $n = 5$), followed by hypertension (1.3%; $n = 4$). Suggestions for avoiding category D and X DDIs included: changing the immunosuppressant dosage, using paracetamol instead of non-steroidal anti-inflammatory drugs, and interrupting atorvastatin. The number of drugs prescribed and having been prescribed TAC was associated with an increased risk of real DDIs. There are many potential DDIs described in the literature but only a small percentage proved to be real DDIs, based on the patients´ outcomes.

KEYWORDS
adverse drug events, clinically relevant, drug–drug interactions, immunosuppressants, prevalence, transplant

Principal Investigator: The authors confirm that the principal investigator for this paper is Ana Isabel Gago-Sánchez and that she had direct clinical responsibility for patients.

1 | INTRODUCTION

The objective of immunosuppressive treatments is to prevent or reverse rejection episodes by combining drugs with various mechanisms of action.[1,2] The clinical efficacy of immunosuppressive therapy depends on the drugs reaching an appropriate blood concentration at their sites of action. Factors that may prevent this concentration from being maintained and the drug from being able to act properly include drug–drug interactions (DDIs) that occur with other drugs administered simultaneously.[3]

In transplant patients, the risk of interaction is high, due to the fact that these patients are polymedicated, and the likelihood of interactions increases with the number of drugs administered.[4,5] Because of polypharmacy and immunosuppressants with a narrow therapeutic window, transplant patients are likely to be particularly vulnerable to adverse drug events (ADEs) caused by DDIs.[6] The addition or withdrawal of a drug capable of modifying the pharmacokinetics of immunosuppressant drugs should be monitored closely for possible alterations in blood concentrations of the latter.[7,8] Therapeutic drug monitoring of immunosuppressant blood concentrations is very useful in the handling of DDIs.[9]

Interactions are therefore a crucial aspect of transplant pharmacotherapy, because of their clinical importance and incidence. In published studies in bone marrow transplant patients, the prevalence of potential interactions with clinical relevance ranged from 21.4%[10] to 82.5%.[11] Andrés González et al.[12] reported a prevalence of interactions of 84.1% in liver transplant patients. Julia Amkreutz et al.[13] found 99 potentially severe interactions per 100 patient days in kidney transplant patients. Although several studies have reported the prevalence of potential DDIs (pDDIs), evidence on the real clinically manifested DDIs is scarce in transplant patients.

Future studies using a prospective design would be better suited to the identification and resolution of clinical manifestations caused by DDIs and should focus on risk factors to help clinicians and pharmacists identify patients at risk.

Drug interaction programs are acknowledged as a fundamental tool to alert physicians to pDDIs. As these databases contain a large number of DDIs, there may be excessive and nonspecific alerts that lack focus on the clinical relevance and correct management of DDIs.[14] It seems that the use of clinical decision support systems, such as an assisted electronic prescription computer system for monitoring and reporting DDIs, as well as inclusion of a clinical pharmacist as a member of the multidisciplinary healthcare team, can contribute to more accurate identification of DDIs.[15]

A large number of pDDIs can be observed in drug interaction programs, immunosuppressive drug data sheets and in the literature, but they do not always have clinical implications. It would be useful to know which ones have a clinical impact on transplant patients becoming real DDIs. Few studies have assessed its clinical relevance.

The main objective of this study was to determine the prevalence of DDIs between immunosuppressants and other drugs with a real clinical impact on transplant patients. Secondary objectives were to categorize the types of DDIs, identify the drugs involved, describe the pharmacist's interventions, and determine the risk factors associated with the increased likelihood of clinically significant DDIs.

What is already known about this subject

- Transplant patients are likely to be particularly vulnerable to adverse drug events (ADEs) caused by drug–drug interactions (DDIs) because of polypharmacy and immunosuppressants with a narrow therapeutic window that are commonly used in this population.
- Therapeutic monitoring of immunosuppressant blood concentrations is useful in the handling of DDIs.
- There are many potential DDIs (pDDIs) described in immunosuppressive drug datasheets, literature, and drug interaction programs, but they do not always have clinical implications, studies that go further than measuring pDDIs are critically needed to determine the impact of DDIs on patient safety.

What this study adds

- Although many pDDIs are described in the literature, a relatively small number of all identified pDDIs proved to be real DDIs expressed in terms of patient outcomes that were detected by determining variations in dose, trough immunosuppressant blood concentrations, and/or ADEs caused by real DDIs.
- This is one of the first published studies to investigate the prevalence of real DDIs in transplant recipients and includes all types of transplantation.
- Immunosuppressive drugs administered with antifungal azoles and tacrolimus with nifedipine have a great clinical impact due to fluctuation in trough immunosuppressant blood concentrations outside the therapeutic range and ADEs (nephrotoxicity, hypertension) in patients.
- The number of drugs prescribed and having been prescribed tacrolimus were associated with an increased risk of real DDIs.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

We conducted a prospective, observational 1-year study (February 1, 2018 to February 1, 2019) at a 1407-bed tertiary hospital (Hospital Universitario Reina Sofia, Córdoba (Spain)) where lung, heart, kidney, bone marrow, and liver transplants are performed.

The study included all adult (aged 18 years and over) heart, lung, kidney, liver, or bone marrow hospitalized transplant patients, who had been prescribed at least one immunosuppressive drug: cyclosporine (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF),

everolimus (EVE), and/or sirolimus (SRL). The patients were enrolled after stable graft function had been achieved. The clinical pharmacist analyzed the DDIs that occurred during the transplant hospitalization until discharge from hospital.

Demographic and clinical data were obtained from the electronic medical record.

The trough immunosuppressant blood concentrations (C_0) of the patients were analyzed daily during hospitalization at the pharmacy pharmacokinetics unit. Immunosuppressant doses were adjusted to maintain target C_0 based on our hospital protocols. The whole blood concentrations of TAC, CsA, and SRL were measured by chemiluminescence with the ARCHITECT*i*system (Abbott). The CEDIA® Mycophenolic Acid Immunoassay (Thermo Fisher Scientific) was used to measure plasma MPA concentrations and Quantitative Microsphere System (QMS) everolimus (Thermo Fisher Scientific) was used to determine EVE whole blood concentrations.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.[16] Informed consent was obtained from all individual participants included in the study. The study was approved by the Local Ethics Committee at the Hospital Universitario Reina Sofía, Córdoba (Spain) before the study began.

2.2 | Identification of pDDIs and real DDIs

The pDDI was defined as "the theoretical possibility of one drug to interact with another when they are administered together".[17]

The pDDIs with clinical significance (severity of interaction: category moderate-mayor-severe) for each of the immunosuppressive drugs were identified and selected through an exhaustive review of drug interaction programs (Lexicomp,[18] Micromedex,[19] Medscape,[20] and Database of the General Council of Official Associations of Pharmacists Spain [BOT Plus][21]), drug data sheets,[22] and tertiary sources.[23,24] In case of discrepancy, we selected the most restrictive classification.

Once pDDIs were selected to avoid unnecessary alarms, they were integrated into the Hospital's the electronic assisted prescribing program (FarmaTools®, comprehensive hospital management tool) which made it possible to generate a real-time alert message to the prescribing physician and the pharmacist in the event of a prescription showed pDDIs between drugs prescribed and immunosuppressants.

All prescription lines were checked by the pharmacist through electronic assisted prescribing, and all pDDIs detected were recorded in pairs.

To assess whether these pDDIs could have a real clinical impact, and therefore, become real DDIs, the patients' medical records were reviewed for data on the monitoring of immunosuppressant blood concentrations, and ADEs caused by DDIs. The pharmacist carried out a detailed review of each patient considering all clinical information (such as age, comorbidities, treatment dose, change in immunosuppressive drug concentration). Clinically manifested DDI was confirmed by laboratory tests and/or patient signs and symptoms. The real DDI was identified if it resulted in drug withdrawal, variation of C_0, and/or when it caused ADEs.

If the pharmacist, in consensus with the physician, determined variation of C_0 and/or an adverse patient outcome, the Drug Interaction Probability Scale (DIPS) tool[25] was applied to assess the likelihood of a causal relationship between a pDDI and an event, those probable (5 to 8 points) or highly probable (>8 points) were considered real DDIs.

The clinical importance of real DDI was expressed in terms of patient outcomes: percentage of patients with ADEs due to real DDIs.

Clinical decision guidelines were used to define ADEs such as nephrotoxicity,[26] hyperglycemia,[27] hypertension,[28] and rhabdomyolysis.[29]

The role of the hospital pharmacist was to manage these real DDIs together with the prescribing physician. In the presence of real DDI, with a high degree of probability of negative consequences for the patient, the pharmacist informed the physician by making the appropriate recommendation in the form of a detailed report and proposing alternative therapeutic strategies to improve the clinical outcomes of transplanted patients.

The DDIs we found were classified as C, D, or X according to Lexi-Interact rating (C = monitor therapy, D = consider therapy modification, X = avoid combination) (Table S1). Drug interactions rated as A (no known interaction) or B (no action needed) were excluded from the analysis.

2.3 | Statistical analysis

A descriptive study of the variables was performed, calculating frequencies for the qualitative variables and arithmetic mean and standard deviation (SD) for the quantitative variables. The 95% confidence interval (CI 95%) was calculated.

Considering the real interaction variable (yes/no) as a dependent variable, univariate logistic regressions were performed to establish the relationship of each of the potentially associated variables. The degree of association was estimated using the odds ratio (OR) and the CI 95%. Using the Wald statistic, the variables with $p \geq .15$ were eliminated from the model one by one and the reduced model was compared with the model that included the eliminated variables using the likelihood-ratio (*G*-statistic) test. Possible interactions between the variables were studied through a significant change in the likelihood logarithm when the interaction was introduced. Variables with a $p > .05$ were studied as possible confounding factors. The Hosmer–Lemeshow statistic was used to assess the goodness of fit.

A multiple linear regression model was performed to identify the factors associated with the main variable: number of real interactions. Previously, the corresponding univariate linear regression analyses of each of the variables introduced in the multiple model were made. Through the Student's *t*-statistic, the variables with $p \geq .15$ were

eliminated from the model one by one. Possible interactions between the variables of the model were studied. Variables with a $p > .05$ were studied as possible confounding factors. The collinearity between independent variables was assessed using the inflation factor of the variance. The independence, normality, and homoscedasticity of the model residues were analyzed using the Durbin–Watson and Shapiro–Wilk tests and the scatter plot between the residual and estimated values, respectively. The corrected determination coefficient (R^2) was used to assess the goodness of fit.

All contrasts performed were bilateral and those with $p < .05$ were considered significant.

The data were collected, processed, and analyzed using the Statistical Package for Social Sciences (SPSS) package v. 25.0 (IBM Corp.).

3 | RESULTS

A total of 309 transplant patients were included. Their mean age was 52.0 ± 14.7 years, with a range of 18–79 years, and 69.9% ($n = 216$) were male. The mean number of drugs prescribed was 12.4 ± 3.6, with a range of 5–27 drugs. The clinical and demographic characteristics of the cohort are presented in Table 1.

Real DDIs were detected in 67 patients, and the prevalence was therefore 21.7%.

The number of real DDIs between immunosuppressants and other drugs was 79 (involving 21 different drug interaction pairs): 72 real DDIs causing immunosuppressant -C_0 modification with ADEs in 15 patients (Table 2), and 7 real DDIs with no variation in C_0 but ADEs in 7 patients by potentiation of toxicity.

The most frequent type of real DDI was category D (54; 68.4%), followed by C (22; 27.8%) and X (3; 3.8%). The most frequent immunosuppressant involved in real DDIs was TAC with 39 real DDIs (49.4%) (24 of severity D and 15 of severity C), followed by CsA with 33 real DDIs (41.7%) (25 of category D, 5 of category C, and 3 of category X). EVE had 6 real DDIs (7.6%) (4 of category D, and 2 of category C), and SRL had 1 real DDI (1.3%) (severity D). No real DDIs were detected for MMF.

All the patients included in the study presented some pDDIs. The number of pDDIs with immunosuppressants was 609 (involving 68 different drug interaction pairs). The type of pDDIs most frequent was category C (413; 67.8%), followed by D (167; 27.4%) and X (29; 4.8%). The most frequent immunosuppressant involved in pDDIs was CsA with 338 pDDIs (55.5%) (222 with severity C, 91 with D, and 25 with X), followed by TAC with 204 pDDIs (33.5%) (140 with severity C, 60 with D, and 4 with X), MMF with 58 pDDIs (9.6%) (48 with severity C, and 10 with D), EVE with 7 pDDIs (1.1%) (4 of category D, and 3 category C), and SRL with 2 pDDIs (0.3%), both category D. Details of the drug pairs involved in pDDIs according to the immunosuppressive drug administered and DDI severity by Lexi-Interact rating, are presented in Table S2.

When analyzing real DDIs in clinical practice, it was observed that the azole antifungal therapeutic group when it was administered with immunosuppressors, the C_0 of all of them (with the exception of MMF) increased. Some patients required a dose decrease of the immunosuppressant considering C_0 to maintain concentrations within the therapeutic range. Voriconazole and fluconazole were the antifungal drugs that showed the most real DDIs. No patients were treated with posaconazole or isavuconazole. Of the 38 pDDIs voriconazole–CsA pair, 20 (52.6%) were real DDIs, and

TABLE 1 Clinical and demographic characteristics of the cohort

TOTAL *n*	309
Gender *n* (%) Male	216 (69.9)
Age (years) Mean ± SD (range)	52.0 ± 14.7 (18–79)
Hospital stay (days) Mean ± SD (range)	23 ± 7.2 (6–42)
Time post-transplantation (days) Mean ± SD (range)	42 ± 8.2 (30–82)
Follow-up period (days) Mean ± SD (range)	20 ± 8.4 (9–45)
Causes of hospitalization *n* (%)	
De novo transplant	132 (42.7)
Fever	64 (20.7)
Diarrhea	30 (9.7)
Respiratory infection	28 (15.5)
Hypertension	17 (5.8)
Urinary infection	8 (5.5)
Others	30 (9.7)
Comorbidities n (%)	
Hypertension	103 (33.3)
Diabetes mellitus	90 (29.1)
Dyslipidemia	72 (23.3)
Coronary heart disease	30 (9.7)
Infectious disease	25 (8.1)
Connective tissue disease	10 (3.2)
Hyperuricemia	7 (2.3)
Type of transplant n (%)	
Kidney transplant	116 (37.5)
Liver transplant	59 (19.2)
Bone marrow transplant	49 (15.8)
Lung transplant	46 (14.9)
Heart transplant	39 (12.6)
Prescribed medications per patient[a] n (%)	
4–6	26 (8.4)
7–9	123 (39.8)
≥10	160 (51.8)
Prescribed immunosuppressive drug n (%)	
Tacrolimus	150 (48.5)
Cyclosporine	112 (36.2)
Mycophenolate mofetil	99 (32.1)
Everolimus	10 (3.2)
Sirolimus	2 (0.6)

[a]Prescribed medications per patient: concomitant medications other than immunosuppressants.

TABLE 2 Real drug–drug interactions: number of real interactions leading to immunosuppressant -C_0 modification, with and without dose adjustment (N° RI), number of patients with adverse drug events (ADEs), mean ± standard deviation (SD) daily immunosuppressant dose (D), trough immunosuppressant blood concentrations (C), and C/D ratio and without/with interacting drug

	Cyclosporine				*Tacrolimus*				*Everolimus*				*Sirolimus*			
	N^O RI(ADEs)	*D Mean ± SD*	*C Mean ± SD*	*C/D ratio Mean ± SD*	*N^O RI(ADEs)*	*D Mean ± SD*	*C Mean ± SD*	*C/D ratio Mean ± SD*	*N^O RI(ADEs)*	*D Mean ± SD*	*C Mean ± SD*	*C/D ratio Mean ± SD*	*N^O RI(ADEs)*	*D Mean ± SD*	*C Mean ± SD*	*C/D ratio Mean ± SD*
Without allopurinol	1 (0)	125	60.9	0.4	-	-	-	-	-	-	-	-	-	-	-	-
With allopurinol		100	92.6	0.9		-	-	-		-	-	-		-	-	-
Without amiodarone	-	-	-	-	1 (0)	0.5	13	26	-	-	-	-	-	-	-	-
With amiodarone		-	-	-		0.5	20	40		-	-	-		-	-	-
Without diltiazem	-	-	-	-	2 (0)	11 ± 9.9	14.2 ± 1.3	2.2 ± 2.1	-	-	-	-	-	-	-	-
With diltiazem		-	-	-		6 ± 5.6	11.2 ± 0.1	3.3 ± 3.1		-	-	-		-	-	-
Without fluconazole	2 (0)	210 ± 56.5	175.1 ± 106.3	0.8 ± 0.3	11 (2)	6.4 ± 3.1*	9.1 ± 4.4*	1.9 ± 1.5*	2 (0)	2.8 ± 3.0	3.2 ± 0.1	2.5 ± 2.7	1(0)	1	7.7	7.7
With fluconazole		162.5 ± 17.7	286.5 ± 112.7	1.7 ± 0.5		5.3 ± 2.9*	15.7 ± 5.7*	4.5 ± 4.8*		2.2 ± 2.5	8.9 ± 2.0	11.3 ± 13.3		1	11	11
Without itraconazole	.	-	-	-	1 (0)	4	8.4	2.1	-	-	-	-	-	-	-	-
With itraconazole		-	-	-		3	10.5	3.5		-	-	-		-	-	-
Without nifedipine	.	-	-	-	10 (2)	9.5 ± 4.4*	12.9 ± 6.6*	1.5 ± 0.7*	-	-	-	-	-	-	-	-
With nifedipine		-	-	-		7.8 ± 4.1*	14.4 ± 13.6*	2.6 ± 3.3*		-	-	-		-	-	-
Without omeprazole	2 (0)	225 ± 106.1	133.5 ± 36.9	0.6 ± 0.1	-	-	-	-	-	-	-	-	-	-	-	-
With omeprazole		225 ± 106.1	227.9 ± 132.7	0.9 ± 0.1		-	-	-		-	-	-		-	-	-
Without phenytoin	3 (0)	140 ± 42.4	146.3 ± 6.4	1.1 ± 0.4	-	-	-	-	-	-	-	-	-	-	-	-
With phenytoin		165 ± 35.3	74 ± 23.4	0.4 ± 0.1		-	-	-		-	-	-		-	-	-
Without rifampicin	1 (0)	50	65.8	1.3	1(0)	1	2.1	2.1	1 (0)	0.5	3.2	6.4	-	-	-	-
With rifampicin		150	17.4	0.1		1	0.1	0.1		0.5	1.6	3.2		-	-	-
Without voriconazole	20 (8)	281.0 ± 134.7*	216.8 ± 129.1*	0.9 ± 0.9*	11(3)	6.1 ± 3.3*	9.1 ± 4.4*	2.1 ± 1.7*	2 (0)	1.5 ± 0.0	3.7 ± 0.6	2.4 ± 0.3	-	-	-	-
With voriconazole		219.7 ± 98.8*	297.9 ± 86.2*	1.5 ± 0.6*		2.8 ± 1.6*	14.5 ± 4.7*	7.1 ± 4.7*		1 ± 0.0	9.4 ± 0.4	9.4 ± 0.4		-	-	-

Abbreviations: C/D ratio, trough immunosuppressant blood concentration (unit of measurement: ng/ml) / daily immunosuppressant dose (unit of measurement: mg); C, trough immunosuppressant blood concentration; D, daily immunosuppressant dose; Mean ± SD, mean ± standard deviation; N^0 RI(ADEs), number of real interaction (adverse drug events).

[a]Statistically significant difference: * $p < .01$.

of the 23 pDDIs voriconazole–TAC pair, 11 (47.8%) were real DDIs. Fluconazole increased C_0 especially when administered with TAC, of the 25 pDDIs fluconazol–TAC pair, 11 (44%) were real DDIs. All of the above real DDIs were classified with severity D by Lexi-Interact rating. As shown in Table 2, some patients experienced ADEs.

Another real DDI of clinical importance was that produced by nifedipine–TAC pair. Of the 59 pDDIs, 10 (16.9%) were real DDIs (severity C), as they all increased C_0, of these, produced ADEs in 2 patients despite the lowering of the dose of the TAC.

Rifampicin and phenytoin also produced real DDIs by inducing a decrease in C_0 when administered together with CsA, TAC, or EVE without ADEs.

Although omeprazole produced a high number of pDDIs with CsA (78), only 2 (2.5%) of them showed a real DDI (severity C), the C_0 of CsA increased outside the therapeutic range without causing ADEs.

The atorvasatin–CsA pair, diclofenac–CsA pair, naproxen–CsA pair, and spironolactone–TAC pair produced real DDIs with no variation in C_0 but with ADEs due to potentiation of toxicity.

Real DDIs caused ADEs in 22 patients. The most common clinical outcome was nephrotoxicity (1.6%; $n = 5$), followed by hypertension (1.3%; $n = 4$). Table 3 presents ADEs caused by real DDIs in patients and management of these toxicities with the intervention of the clinical pharmacist.

Most of the pharmacist's recommendations for management of real DDIs category C referred to close monitoring of immunosuppressant C_0, blood pressure, electrolytes, and blood glucose. Suggestions for avoiding occurrence of types D and X included changing the immunosuppressant dosage, considering therapy modification, using paracetamol instead of non-steroidal anti-inflammatory drugs, and interrupting atorvastatin.

The multiple logistic regression model used to analyze the risk factors associated with the occurrence of real DDIs in patients concluded that the number of drugs prescribed and having been prescribed TAC were associated with an increased risk of real DDIs. When multiple analyses using the multiple linear regression model were performed to identify the factors related to the number of real DDIs, it was observed that for each additional pDDI the patient had, the number of real DDIs increased by 0.09. It was also seen that if the patient had been prescribed TAC the number of real DDIs increased by 0.18 (Table 4).

4 | DISCUSSION

The target population selected to carry out the study was considered necessary, since transplant patients must be given immunosuppressive drugs. These drugs have a narrow therapeutic range and are metabolized primarily in the liver and intestinal mucosa by 3A isoenzymes of cytochrome P450 (CYP3A4 and CYP3A5) and P-glycoprotein.

In our study, all the patients included (100%) showed some moderate or greater degree of pDDIs between the immunosuppressants and other drugs. However, the prevalence of real DDIs was 21.7%. Most studies on this subject do not focus on the prevalence of clinically relevant DDIs.[30,31] A meta-analysis[32] aimed to determine the prevalence of clinically manifested DDIs in hospitalized patients identified 5999 studies. Of these, only 10 studies met the inclusion criteria and none of them included hospitalized transplant recipients. The definition for DDIs has varied from one study to another depending on the applied assessment methods, populations and study settings, thus resulting in a wide range of prevalence. This makes it difficult to compare DDIs between studies. Few researchers have evaluated the severity of DDIs.

Prospective, population-based studies are very useful to assess the consequences of DDIs in clinical practice. After a literature search, we did not find any prospective, observational studies similar to ours that evaluated real DDIs in transplant patients. A unique aspect of our study is its pragmatic nature and the fact we investigated the real effects of the identified pDDIs. In addition, this is the first published study to investigate the prevalence of real DDIs in hospitalized transplant patients including all types of transplantation.

Tacrolimus was the most widely prescribed immunosuppressive drug and the one most frequently involved in real DDIs, but CsA was the immunosuppressant most frequently involved in pDDIs. Both are highly dependent on CYP3A4 and CYP3A5, and this factor, in addition to frequency of prescribing, might predispose patients receiving these drugs to experience more frequent DDIs.

We found that 68.4% of the real DDIs were type D, requiring aggressive monitoring and empiric dosage changes. However, the most prevalent category of pDDIs observed in our study was C. Type C DDIs will rarely cause serious or fatal consequences, but need careful monitoring to minimize the potential negative outcomes of these interactions.

Infections in transplant patients are a common complication, accounting for 15% to 20% of deaths.[33] Many of the antimicrobial agents used to treat or prevent such infections have certain pharmacokinetic characteristics that predispose to DDIs.[34] All antifungal azoles inhibit the metabolism of CsA, TAC, SRL, and EVE due to inhibition of the CYP3A4 enzyme.[35,36]

Voriconazole and fluconazole were the antifungal drugs that showed the most real DDIs in our patients. No patient was prescribed posaconazole or isavuconazole because at the time of the study neither of these azoles were included in the hospital's pharmacotherapeutic guide.

Voriconazole produced real DDIs, especially when administered with CsA. Although, this real DDI was already known[37,38] the increase in levels in our study was very high. We should therefore consider further decreasing the dose of CsA to avoid this excessive increase in levels. The labeling of voriconazole emphasizes that empirical dose reductions of CsA (reduce by half) and TAC (reduce by one-third) are recommended upon initiation of voriconazole therapy.[39] It should be noted that voriconazole exhibits nonlinear pharmacokinetics, such that exposure increases disproportionately with dosage. The magnitude of DDI is highly variable and a priori dose adjustment may be insufficient.[40]

TABLE 3 Adverse drug events caused by real drug–drug interactions in patients and management of these toxicities

Adverse drug event	Real DDI DIPS score (Causal relationship)	Severity[a]	N^O Patients (N^O *real DDI with change in* C_0)	Type of transplant (n)	Time (days) to develop ADEs after drug combination Mean±SD (range)	Summary	Management Clinical pharmacist intervention
Nephrotoxicity	CsA–voriconazole Score = 7 (Probable)	D	2 (2)	Bone marrow transplant (2)	5 ± 3.2 (4–9)	Increased blood levels of CsA causing renal dysfunction	Reduce dose of CsA, monitor CsA concentrations and renal function
	TAC–voriconazole Score = 6 (Probable)	D	1 (1)	Lung transplant (1)	6	Increased blood levels of TAC causing renal dysfunction	Reduce dose of TAC, monitor TAC concentrations and renal function
	CsA–diclofenac Score = 7 (Probable)	D	1 (0)	Heart transplant (1)	8	Potentiation of nephrotoxicity	Consider therapy modification: paracetamol instead of diclofenac
	CsA–naproxen Score = 5 (Probable)	D	1 (0)	Heart transplant (1)	7	Potentiation of nephrotoxicity	Consider therapy modification: paracetamol instead of naproxen
Hypertension	CsA-voriconazole Score = 7 (Probable)	D	3 (3)	Bone marrow transplant (2) Lung transplant (1)	7 ± 4.3 (3–9)	Increased blood levels of CsA causing hypertension	Reduce dose of CsA, monitor CsA concentrations and blood pressure
	TAC–fluconazole Score = 6 (Probable)	D	1 (1)	Lung transplant (1)	5	Increased blood levels of TAC causing hypertension	Reduce dose of TAC, monitor TAC concentrations and blood pressure
Hyperkalemia	TAC-spironolactone Score = 6 (Probable)	C	2 (0)	Liver transplant (2)	6 ± 2.3 (4–7)	Enhanced hyperkalemic effect.	Monitor potassium
	TAC–voriconazole Score = 7 (Probable)	D	1 (1)	Lung transplant (1)	4	Increased blood levels of CsA causing hyperkalemia	Reduce dose of TAC, monitor TAC concentrations and potassium
Rhabdomyolysis	CsA–atorvastatin Score = 5 (Probable)	X	3 (0)	Kidney transplant (2) Bone marrow transplant (1)	8 ± 4.4 (4–12)	Increased blood levels of creatine kinase, muscle symptoms, creatinine elevation and myoglobinuria. Potentiation of toxicity of atorvastatin.	Interrupt atorvastatin
Hirsutism	CsA–voriconazole Score = 7 (Probable)	D	3 (3)	Bone marrow transplant (2) Lung transplant (1)	10 ± 4.7 (6–17)	Increased blood levels of CsA.	Reduce dose of CsA and monitor CsA
Hyperglycemia	TAC–fluconazole Score = 6 (Probable)	D	1 (1)	Heart transplant (1)	9	Increased blood levels of TAC causing hyperglycemia.	Reduce dose of TAC, monitor TAC concentrations and blood glucose
	TAC–voriconazole Score = 6 (Probable)	D	1 (1)	Kidney transplant (1)	8	Increased blood levels of TAC causing hyperglycemia.	Reduce dose of TAC, monitor TAC concentrations and blood glucose
Gingival hyperplasia	TAC–nifedipine Score = 7 (Probable)	C	2 (2)	Kidney transplant (2)	12 ± 3.7 (7–16)	Increased blood levels of TAC. Mean time to develop ADEs after drug combination.	Reduce dose of TAC, and monitor TAC concentrations

Abbreviations: CsA, cyclosporine; C_0, trough immunosuppressant blood concentrations; n, number of patients; DIPS, drug interaction probability scale; TAC, tacrolimus.

[a]Severity according to the Lexi-Interact ratings.

TABLE 4 Logistic regression analysis and linear regression analysis for factors associated with real drug–drug interactions

Variables	Univariate analysis OR (95% CI)	*p*	multiple analysis OR (95% CI)	*p*	Univariate analysis ß (95% CI)	*p*	multiple analysis ß (95% CI)	*p*
Age (years)	0.98 (0.96 to 0.99)	.021	0.98 (0.96 to 0.99)	.032	−0.01 (−0.00 to 0.00)	.385		
Female	0.74 (0.40 to 1.37)	.342			0.06 (−0.09 to 0.21)	.442		
Number of prescribed drugs	1.11 (1.03 to 1.20)	.007	1.09 (1.01 to 1.19)	.030	0.01 (−0.01 to 0.03)	.417		
Number of potential interactions	1.20 (0.99 to 1.44)	.058			0.05 (−0.00 to 0.09)	.056	0.09 (0.04 to 1.15)	.001
Cyclosporine	1.35 (0.78 to 2.35)	.287			−0.01 (−0.14 to 0.13)	.934		
Everolimus	5.85 (1.60 to 21.39)	.008	7.86 (1.93 to 31.99)	.004	0.28 (0.07 to 0.50)	.011	0.37 (0.17 to 0.58)	.001
Mycophenolate mofetil	0.60 (0.32 to 1.12)	.108			0.07 (−0.09 to 0.22)	.387		
Sirolimus	3.65 (0.23 to 59.16)	.362	26.45 (1.36 to 513.6)	.030	−0.08 (−0.61 to 0.46)	.779		
Tacrolimus	1.30 (0.76 to 2.24)	.338	3.56 (1.36 to 9.33)	.010	0.02 (−0.11 to 1.15)	.774	0.18 (0.04 to 0.32)	.015

[a]Likelihood-ratio *G*-test: 26.084 ($p < .001$); Hosmer–Lemeshow chi-square test: 9.60 ($p = .294$).

[b]Coefficient of determination (R^2) = 0.254.

Voriconazole has been shown to produce a higher increase in TAC blood concentrations than fluconazole, because it is a stronger inhibitor of CYP3A4.[41–43] In our study, the dose of TAC was preventively reduced by a higher percentage in patients treated with voriconazole than with fluconazole.

Another real DDI of clinical importance was that produced by nifedipine–TAC pair. DDIs between nifedipine and TAC, both competitive substrates of the CYP3A4 and CYP3A5 system, as well as P-gp, can result in a rapid increase in blood concentrations. Yilei Yang et al.[44] showed the co-administrated nifedipine and CYP3A5*3/*3 homozygotes significantly increased tacrolimus concentrations.

Although many pDDIs are described in the literature, this study found that a relatively small number of all identified pDDIs proved to be real DDIs. Clinical significance of a DDI is expressed in terms of patient outcomes, not the presence of pDDIs in drug interaction programs, which may repeat incorrect DDIs warnings. For example, when analyzing DDIs with omeprazole–CsA pair, we observed that although a high number of pDDIs was recorded, only two showed real DDIs, so the omeprazole interferes very little with CsA blood levels. A previous study of omeprazole-CsA interaction in renal transplant patients[45] also found no significant alteration of C_0.

There is a wide variety of databases that allow the detection of pDDIs.[46–49] We have integrated the most significant pDDIs in an assisted prescription program to facilitate this detection. To this end, we have previously analyzed four databases of interactions and in order to compare and try to correct possible discrepancies between them, we have consulted technical data sheets and tertiary sources. This integration allows the physician to detect pDDIs at the time of prescribing, without excessive alarms[14,50] reducing alert fatigue, and allowing the pharmacist to validate the prescription of all transplanted patients admitted to the hospital. In addition, once the integration is complete, the assisted prescribing system enables an update in case new clinically important pDDIs appear in the literature.

This is an important starting point for advanced forms of clinical decision-support systems, which should help the physician and pharmacist to identify important pDDIs without generating clinically irrelevant alerts. The studies evaluated in the meta-analysis[32] used a single source to detect pDDI, without integration into an assisted prescribing program.

The DDIs were classified according to Lexi-Interact rating which is well-known to health professionals and has been cited in different studies.[51–53]

The participation of clinical pharmacist and therapeutic drug monitoring are considered helpful in managing DDIs.[54,55] In patients with C_0 variation, the pharmacist informed the physician with the appropriate recommendations. In most patients, the dose of immunosuppressant was preemptively modified to maintain C_0 within the therapeutic range, therefore, not all patients, with real DDIs due to C_0 alteration, suffered toxicity. Adverse reactions related to DDIs were decreased by the preventive actions, but some patients still experienced ADEs.

It was not always clear whether the patient's adverse outcome or C_0 variation was caused by DDI. To address this, clinically manifested DDI was confirmed by laboratory tests and/or signs and symptoms were documented in medical records. Further investigations were carried out as necessary to exclude alternative causes

of DDI. In addition, there was a consensus between the physician and pharmacist to make a decision and the DIPS algorithm was used, which is able to assist in the assessment of causality in clinically relevant observed DDIs in an objective, reliable and transparent manner.

Factors affecting the frequency and severity of DDIs of immunosuppressive drugs may be linked to the therapy (concomitant drugs and polymedication) or to the patient (age, gender, and inter- and intraindividual variability).[56,57] In our study, the number of drugs prescribed and the administration of TAC showed a statistically significant association with the occurrence of real DDIs. In line with our research, many studies found a relationship between the prevalence of DDIs and the number of prescribed medications.[58] Our study also showed that being prescribed EVE or SRL was also a risk factor for real DDIs, but we must point out that although the majority of patients with these drugs had real DDIs, the sample of patients was very small.

5 | LIMITATIONS

The study has a number of limitations due to the complexity of studying DDIs in transplant recipients, as these individuals are at high risk of pharmacotherapeutic morbidity due to the complications inherent to their polytherapy.

Inter-and intraindividual variability in C_0 should be considered. In addition, the terminal half-life of the drugs affects the duration of any DDIs and may lead to variability in the times taken to reach steady-state concentrations after dose adjustments, which might contribute to variation in levels. We must point out that immunosuppressant drugs may not demonstrate linear pharmacokinetic profiles, making it difficult to draw direct conclusions on the relationship of percentage dose change to percentage level variability.

Although interactions were considered by pairs of drugs, multiple interactions occur between three or more drugs, and a limitation of the study is that it does not consider the influence of an additional drug on the manifestations and consequences of DDIs.

This is a single-center study but it would be useful to conduct a multicenter study for professionals to reach a consensus to ensure that important interactions in patient care are appropriately selected. Standardization of DDI definitions and research methods are required to allow meaningful prevalence rates to be obtained and compared.

6 | CONCLUSIONS

In conclusion, there are many pDDIs described in the literature, but in our study only a small percentage proved to be real DDIs, expressed in terms of patient outcomes that were detected by determining variations in dose, $C_{0,}$ and/or ADEs caused by real DDIs.

Adverse outcomes resulting from DDIs in the majority of patients can be prevented with an appropriate monitoring plan and dosage adjustments of interacting agents. Monitoring blood drug levels enhances dosage management in these patients.

The results enable us to identify the pharmacological groups that caused real DDIs. Immunosuppressive drugs administered with azole and TAC with nifedipine show a high risk of producing clinically significant interactions.

Multiple analysis of factors related to real DDIs concluded that the number of drugs prescribed and the administration of TAC, were associated with an increased risk of real DDIs. It was also observed that for each additional potential interaction a patient had, the number of real interactions increased by 0.09.

An effective software tool, such as an assisted electronic prescribing program, is needed to facilitate screening by pre-selecting potential clinically important interactions and to reduce alert fatigue by highlighting only the most serious alerts.

Because of their knowledge of pharmacotherapy and monitoring of blood drug levels, pharmacists play a crucial role in detecting DDIs and disseminating information among the multidisciplinary team to educate about DDIs and resultant ADEs in order to prevent harm and ensure patient safety.

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DISCLOSURE

Ana Isabel Gago, Pilar Font, Manuel Cárdenas, María Dolores Aumente, José Ramón Del Prado and Miguel Ángel Calleja declare that they have no conflict of interest.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the Local Ethics Committee at the Hospital Universitario Reina Sofía, Córdoba (Spain) before the study began.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

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