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

Ana Isabel Gago-Sánchez1 | Pilar Font2 | Manuel Cárdenas1 | María Dolores Aumente1 | José Ramón Del Prado1 | Miguel Ángel Calleja3

1Pharmacy Department, Hospital Universitario Reina Sofia/Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/University of Córdoba, Córdoba, Spain
2Rheumatology Department, Hospital Universitario Reina Sofia/Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/University of Córdoba, Córdoba, Spain
3Pharmacy Department, Hospital Universitario Virgen Macarena, Sevilla, Spain

Correspondence
Ana Isabel Gago-Sánchez, Pharmacy Department, Hospital Universitario Reina Sofia, Avda Menéndez Pidal s/n, 14004 Córdoba, Spain.
Email: anai.gago.sspa@juntadeandalucia.es; anagasa91@hotmail.com

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
1 | INTRODUCTION

The objective of immunosuppressive treatments is to prevent or reverse rejection episodes by combining drugs with various mechanisms of action. 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.

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. 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. 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. Therapeutic drug monitoring of immunosuppressant blood concentrations is very useful in the handling of DDIs.

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% to 82.5%. Andrés González et al. reported a prevalence of interactions of 84.1% in liver transplant patients. Julia Amkreutz et al. 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. 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.

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.

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 Sofía, 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® 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. 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.”

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, Micromedex, Medscape, and Database of the General Council of Official Associations of Pharmacists Spain [BOT Plus])²ⁱ, drug data sheets, and tertiary sources. 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 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.

To assess whether these DDIs resulted in clinically significant drug interactions, we classified them as possible (1 point), probable (2 to 4 points), possible (5 to 8 points), and highly probable (>8 points). Those DDIs classified between 0 and 1 point were considered probable, 2 to 4 points were considered possible, and 5 to 8 points were considered definite DDIs.

All patients were monitored by the pharmacist to identify possible DDIs occurring during hospital stay. The pharmacist informed the physician by making the appropriate modification in the treatment plan in case of a real DDI. 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 $p ≥ .15$ 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 $p ≥ .15$ 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 -CsA 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 immunosuppressants, 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 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)                 |

*Prescribed medications per patient: concomitant medications other than immunosuppressants.
|            | Cyclosporine | Tacrolimus | Everolimus | Sirolimus |            |            |            |            |            |            |            |            |            |            |
|------------|--------------|------------|------------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|            | N\(^0\) RI(ADEs) | D | C | C/D ratio | N\(^0\) RI(ADEs) | D | C | C/D ratio | N\(^0\) RI(ADEs) | D | C | C/D ratio | N\(^0\) RI(ADEs) | D | C | C/D ratio |            |            |            |            |            |            |
|            | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |            |            |            |            |            |            |            |            |            |            |            |            |
| Without allopurinol | 1 (0) | 125 | 60.9 | 0.4 | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With allopurinol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without amiodarone | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With amiodarone | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without diltiazem | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With diltiazem | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| 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 | 10 (0) | 1 | 7.7 | 7.7 |            |            |            |            |            |            |            |            |            |            |            |            |
| With fluconazole | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without itraconazole | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With itraconazole | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without nifedipine | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With nifedipine | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without omeprazole | 2 (0) | 225 ± 106.1 | 133.5 ± 36.9 | 0.6 ± 0.1 | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With omeprazole | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Without phenytoin | 3 (0) | 140 ± 42.4 | 146.3 ± 64 | 1.1 ± 0.4 | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| With phenytoin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| 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 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| 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 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |            |            |            |            |            |            |            |            |            |            |            |            |            |            |

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).

\(^*\)Statistically significant difference: * \(p < .01\).
of the 23 pDDIs voriconazole–TAC pair, 11 (47.8%) were real DDIs. Fluconazole increased C0, 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 C0, 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 C0 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 C0 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 C0 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 C0, 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. A meta-analysis 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 DDIs 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. Many of the antimicrobial agents used to treat or prevent such infections have certain pharmacokinetic characteristics that predispose to DDIs. All antifungal azoles inhibit the metabolism of CsA, TAC, SRL, and EVE due to inhibition of the CYP3A4 enzyme.

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 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. 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.
| Adverse drug event | Real DDI DIPS score (Causal relationship) | Severity* | N² Patients (N² real DDI with change in C₀) | 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)         | 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 TAC causing hyperkalemia     | Reduce dose of TAC, monitor TAC concentrations and potassium |
| Rhabdomyolysis    | CsA–atorvastatin Score = 5 (Probable)   | X         | 3 (0) Kidney transplant (2)              | 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)         | 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; C₀, trough immunosuppressant blood concentrations; n, number of patients; DIPS, drug interaction probability scale; TAC, tacrolimus.

*Severity according to the Lexi-Interact ratings.
Voriconazole has been shown to produce a higher increase in TAC blood concentrations than fluconazole, because it is a stronger inhibitor of CYP3A4. 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. showed the co-administration of 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 DDI 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 also found no significant alteration of C0.

There is a wide variety of databases that allow the detection of pDDIs. 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 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 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.

The participation of clinical pharmacist and therapeutic drug monitoring are considered helpful in managing DDIs. In patients with C0 variation, the pharmacist informed the physician with the appropriate recommendations. In most patients, the dose of immunosuppressant was preemptively modified to maintain C0 within the therapeutic range, therefore, not all patients, with real DDIs due to C0 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 C0 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 intra-individual variability). 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. 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 C₀ 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, C₀, 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.

ACKNOWLEDGMENTS

This article is part of the doctoral thesis of Ana Isabel Gago-Sánchez in the Doctoral Program in Pharmacy at the University of Granada, Spain.

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 Sofia, Córdoba (Spain) before the study began.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Ana Isabel Gago-Sánchez https://orcid.org/0000-0002-5674-045X

REFERENCES

1. Wong CJ, Pagalilauan G. Primary care of the solid organ transplant recipient. Med Clin North Am. 2015;99(5):1075-1103.
2. Jasiak NM, Park JM. Immunosuppression in solid-organ transplantation: essentials and practical tips. Crit Care Nurs Q. 2016;39(3):227-240.
3. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med. 2015;13(1):1995-2010.
4. Manitisitkul W, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. Curr Opin Nephrol Hypertens. 2009;18(5):404-411.

5. Dookeeram D, Bidaisee S, Paul JF, et al. Polypharmacy and potential drug-drug interactions in emergency department patients in the Caribbean. Int J Clin Pharm. 2017;39(5):1119-1127.

6. Pejčić A, Janković SM, Opančina V, Babić G, Milosavjević M. Drug-drug interactions in patients receiving hematopoietic stem cell transplantation. Expert Opin Drug Metab Toxicol. 2019;15(1):49-59.

7. Kuypers DR. Influence of interactions between immunosuppressive drugs on therapeutic drug monitoring. Ann Transplant. 2008;13(3):11-18.

8. Page RL II, Mueller SW, Levi ME, Lindenfeld J. Pharmacokinetic drug-drug interactions between calcineurin inhibitors and proliferation signal inhibitors with anti-microbial agents; implications for therapeutic drug monitoring. Heart Lung Transplant. 2011;30(2):124-135.

9. Sparkes T, Lemonovich TL; AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants—guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13510.

10. Guastaldi RB, Reis AM, Figueras A, Secoli SR. Prevalence of potential drug-drug interactions in bone marrow transplant patients. Int J Clin Pharm. 2011;15(2):161-166.

11. Trevisan DD, Silva JB, Oliveira HC, Secoli SR, Lima MH. Prevalence and clinical significance of potential drug-drug interaction in hematopoietic stem cell transplantation. Cancer Chemother Pharmacol. 2015;75(2):393-400.

12. Andrés González C, Romero Jiménez RM, Pérez VS. Drug interactions in liver transplant patients. Eur J Clin Pharm. 2013;15(5):344-350.

13. Amkreutz J, Koch A, Buendgens L, Mühlfeld A, Trautwein C, Eisert A. Prevalence and nature of potential drug-drug interactions among kidney transplant patients in a German intensive care unit. Int J Clin Pharm. 2017;39(5):1128-1139.

14. Zenzipper Straichmann Y, Kurnik D, Matok I, et al. Prescriber response to computerized drug alerts for electronic prescriptions among hospitalized patients. Int J Med Inform. 2017;107:70-75.

15. Peral Aguirregoitia J, Lertxundi Etxebarria U, Martínez Bengoechea MJ, Mora Atorrassagasti O, Franco Lamela E, Gabioldino ZI. Prospective assessment of drug interactions in hospitalized patients using a computer programme. Farm Hosp. 2007;31(2):93-100.

16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194.

17. Morales-Ríos O, Jasso-Gutiérrez L, Reyes-López A, Garduño-Espinosa J, Muñoz-Hernández O. Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico. PLoS One. 2018;13(1):e0190882.

18. Wolters Kluwer. Lexicomp. Database. Available at: https://www.wolterskluwercd.com/lexicomp/online/. Accessed January 07, 2021.

19. IBM. IBM Micromedex with Watson. Database. Available at: https://www.IBM.com/products/micromedex-with-watson. Accessed January 07, 2021.

20. Medscape. Drug interaction checker. Available at: https://reference.medscape.com/drug-interactionchecker. Accessed January 07, 2021.

21. General Council of Official Associations of Pharmacists (Spain). Pharmaceutical knowledge database BOT PLUS. Available at: https://www.portalfarma.com. Accessed January 07, 2021.

22. CIMA. Online Drug Information Center of the Spanish Agency for Medicines and Health Products (AEMPS). Available at: https://cima.aemps.es/cima/público/home.html Accessed January 07, 2021.

23. Tatro DS. Drug interaction facts. Wolters Kluwer Health; 2014.

24. Stockley. Interacciones farmacológicas. 2nd edition. Pharma Editores; 2007.

25. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41(4):674-680.

26. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-c184.

27. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Suppl. 1):S81-S90.

28. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group: 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021-3104.

29. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40(3):567-572.

30. Zheng WY, Richardson LC, Li L, Day RO, Westbrook JI, Baysari MT. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2018;74(1):15-27.

31. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2014;23(5):489-497.

32. Gonzaga de Andrade Santos TN, Mendonça da Cruz Macieira G, Cardoso Sodré Alves BM, et al. Prevalence of clinically manifested drug interactions in hospitalized patients: a systematic review and meta-analysis. PLoS One. 2020;15(7):e0235353.

33. Guastaldi RBF, Secoli SR. Drug interactions of anti-microbial agents used in hematopoietic stem cell transplantation. Rev Lat Am Enfermagem. 2011;19(4):960-967.

34. Glotzbecker B, Duncan C, Aiyea E, Campbell B, Soffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. Biol Blood Marrow Transplant. 2012;18(7):989-1006.

35. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010;30(8):842-854.

36. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy. 2006;26(12):1730-1744.

37. Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. Am J Transplant. 2017;17(9):2372-2380.

38. Lempers VJC, Martial LC, Schreuder MF, et al. Drug-interactions of azole antifungals with selected immunosuppressants in transplant patients: strategies for optimal management in clinical practice. Curr Opin Pharmacol. 2015;24:38-44.

39. Vfend (voriconazole). Online Drug Information Center of the Spanish Agency for. Medicines and Health Products (AEMPS). Available at: https://cima.aemps.es/cima/pdfs/es/ft/79141/Ficha Tecnica._79141.html.pdf. Accessed January 07, 2021.

40. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. Transpl Infect Dis. 2017;19(5):e12751.

41. Kawaoze H, Takiguchi Y, Tanaka H, et al. Change of the blood concentration of tacrolimus after the switch from fluconazole to voriconazole in patients receiving allogeneic hematopoietic stem cell transplantation. Biol Pharm Bull. 2006;29(12):2528-2531.

42. Trifilio SM, Scheetz MH, PI J, Mehta J. Tacrolimus use in adult allo-genic stem cell transplant recipients receiving voriconazole: pre-emptive dose modification and therapeutic drug monitoring. Bone Marrow Transplant. 2010;45(8):1352-1356.
43. Lumlertgul D, Noppakun K, Rojanasthien N, et al. Pharmacokinetic study of the combination of tacrolimus and fluconazole in renal transplant patients. J Med Assoc Thai. 2006;89(suppl 2):S73-S78.

44. Yang Y, Huang X, Shi Y, et al. CYP3A5 genotype-dependent drug-drug interaction between tacrolimus and nifedipine in Chinese renal transplant patients. Front Pharmacol. 2021;5(12):692922.

45. Blohmé I, Idström JP, Andersson T. A study of the interaction between omeprazole and cyclosporine in renal transplant patients. Br J Clin Pharmacol. 1993;35(2):156-160.

46. Amkreutz J, Koch A, Buendgens L, Trautwein C, Eisert A. Clinical decision support systems differ in their ability to identify clinically relevant drug interactions of immunosuppressants in kidney transplant patients. J Clin Pharm Ther. 2017;42(3):276-285.

47. Fung KW, Kapusnik-Uner J, Cunningham J, Higby-Baker S, Bodenreider O. Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. J Am Med Inform Assoc. 2017;24(4):806-812.

48. Tecen-Yucel K, Bayraktar-Ekincioglu A, Yildirim T, Yilmaz SR, Demirkan K, Erdem Y. Assessment of clinically relevant drug interactions by online programs in renal transplant recipients. J Manag Care Spec Pharm. 2020;26(10):1291-1296.

49. Rodríguez-Terol A, Caraballo MO, Palma D, et al. Quality of interaction database management systems. Farm Hosp. 2009;33(3):134-146.

50. Poldor P, Di Giorgio C, Provenzani A. Incidence of potential drug interactions in a transplant centre setting and relevance of electronic alerts for clinical practice support. Inform Prim Care. 2012;20(4):257-262.

51. Moghaddas A, Adib-Majlesi M, Sabzghabaee AM, Hajigholami A, Riechelmann R. Potential drug-drug interactions in hospitalized cancer patients: a report from the Middle-East. J Oncol Pharm Pract. 2021;27(1):46-53.

52. Tavakoli-Ardakani M, Kazemian K, Salamzadeh J, Meh dizadeh M. Potential of drug interactions among hospitalized cancer patients in a developing country. Iran J Pharm Res. 2013;12(Suppl):175-182.

53. Sánchez Muñoz-Torrero JF, Barquilla P, Velasco R, et al. Adverse drug reactions in internal medicine units and associated risk factors. Eur J Clin Pharmacol. 2010;66(12):1257-1264.

54. Duwez M, Chanoine S, Lepelley M, et al. Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study. BMJ Open. 2020;10(11):e041563.

55. Peng CC, Glassman PA, Marks IR, et al. Retrospective drug utilization review: incidence of clinically relevant potential drug-drug interactions in a large ambulatory population. J Manag Care Pharm. 2003;9(6):513-522.

56. Park JW, Roh J-L, Lee S-W, et al. Effect of polypharmacy and potentially inappropriate medications on treatment and posttreatment courses in elderly patients with head and neck cancer. J Cancer Res Clin Oncol. 2016;142(5):1031-1040.

57. Gholaminezhad S, Hadjibabaie M, Gholfami K, et al. Pattern and associated factors of potential drug-drug interactions in both pre- and early post-hematopoietic stem cell transplantation stages at a referral center in the Middle East. Ann Hematol. 2014;93(11):1913-1922.

58. Shafiekhani M, Tarighati S, Mirzaei E, Namazi S. Evaluation and management of drug-drug interactions in patients hospitalized in nephrology and post-transplant wards in a teaching hospital. J Pharm Care. 2020;8(1):16-22.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gago-Sánchez AI, Font P, Cárdenas M, Aumente MD, Del Prado JR, Calleja MÁ. Real clinical impact of drug-drug interactions of immunosuppressants in transplant patients. Pharmacol Res Perspect. 2021;9:e00892. doi:10.1002/prp2.892