Original paper

Interventions performed by clinical pharmacist in the renal transplant ambulatory care

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Abstract

Introduction: The development of new immuno-suppressant agents and other supporting medications has increased the complexity of medical regimes. Therefore, potential drug interactions, adverse reactions and costs may jeopardize a successful outcome. Although pharmacists have been involved in the care of patients after transplants, only a few kidney transplant teams can count with dedicated pharmaceutical services. **Objective**: The goal of this study was to describe the pharmaceutical interventions performed to improve treatment outcomes of patients who underwent kidney transplantation. **Methods**: This study was a randomized clinical trial and was carried out in a specialized transplant hospital in southern Brazil. The clinical pharmacist followed up 64 patients during a period of 12 months and performed interventions when identifying a drug related problem. The pharmaceutical interventions were categorized as "significant", "very significant" or "extremely significant". Medication-related negative outcomes were classified in relation to their effectiveness, safety and necessity. **Results**: Two hundred and twenty-six (226) pharmaceutical interventions were performed, with a mean of 3.25 ± 2.37 per patient. Among them, 159 (70.4%) were patient-oriented, and 67 (29.6%) were health team-oriented. Thirty eight percent were classified as very significant. Frequent pharmaceutical interventions performed were to suggest the reduction of immuno-suppressant doses to the physicians, educate patients with post-transplant diabetes mellitus or in case of skipping doses. One hundred and fourteen (114) medication-related negative outcomes were identified, 43% related to effectiveness, 36% to safety and 21% to necessity. The number of acute rejection confirmed by biopsy was 33 (51.6%). The free survival of acute rejection was 59.4% in the first month, 53.1% in the third month and 48.3% in 12 months. **Conclusions**: The pharmacist has an important role in the ambulatory care of kidney transplant, identifying problems and acting as a major player towards the reduction of medication-related negative outcomes.

Keywords: Ambulatory care, Pharmacists, Immuno-suppressant agents, Treatment outcomes, Brazil.

Intervenções realizadas pelo farmacêutico clínico no ambulatório de transplante renal

Resumo

Introdução: O desenvolvimento de novos agentes imunossupressores e outros medicamentos de suporte têm aumentado à complexidade dos tratamentos. Consequentemente, interações medicamentosas potenciais, reações adversas e custos podem comprometer o resultado terapêutico. Embora os farmacêuticos tenham sido envolvidos no cuidado de pacientes após transplantes, poucas equipes de transplante renal podem contar com serviços farmacêuticos. **Objetivos**: Descrever as intervenções farmacêuticas realizadas para melhorar os resultados do tratamento de pacientes submetidos à transplante renal. **Métodos**: Trata-se de um ensaio clínico randomizado que foi realizado em um hospital especializado em transplantes no sul do Brasil. O farmacêutico clínico acompanhou 64 pacientes durante um período de 12 meses e realizou intervenções quando identificava um problema relacionado a medicamento. As intervenções farmacêuticas foram categorizadas em "significante", "muito significante" ou "extremamente significante". Os Resultados Negativos associados ao uso dos Medicamentos (RNM) foram classificados em relação à efetividade, segurança e necessidade. **Resultados**: Foram realizadas 226 intervenções farmacêuticas, com uma média de 3,25 ± 2,37 por paciente. Entre elas, 159 (70,4%) foram orientadas ao paciente e 67 (29,6%) à equipe de saúde. Trinta e oito por cento foram classificados como muito significantes. Algumas das intervenções farmacêuticas frequentes foram sugerir a redução de dose do imunossupressor para os médicos, educar pacientes com diabetes mellitus pós-transplante ou em caso de omissão de doses. Foram identificados 114 RNM, 43% relacionados à efetividade, 36% à segurança e 21% à necessidade. O número de rejeição aguda confirmada por biópsia foi 33 (51,6%). A sobrevida livre de rejeição aguda foi de 59,4% no primeiro mês, 53,1% no terceiro mês e 48,3% em 12 meses. **Conclusões**: O farmacêutico tem um papel importante no ambulatório de transplante renal, identificando problemas e atuando como um dos principais atores para a redução dos RNM.

Palavras-chave: cuidados ambulatoriais, farmacêuticos, agentes imunossupressores, resultados do tratamento, Brasil.

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Introduction

Late stage renal disease demands substitutive therapy, being the kidney transplant the therapy of choice. When compared to dialysis, kidney transplant proves to be superior in many levels such as morbidity, quality of life level and long-term costs.[1] According to the Brazilian Association of Organ Transplantation, 131 teams performed kidney transplant in 2017, totalizing 5929 transplants. Brazil is the second in absolute number of kidney transplants (among 30 countries), behind only the US.[2]

The development of new immunosuppressant agents and other supporting medicines has increase the complexity of medical regimes. Therefore, potential drug interactions, adverse reactions and costs may jeopardize a successful outcome.[3]

Although pharmacists have been involved in the care of patients after transplants, only a few kidney transplant teams can count with dedicated pharmaceutical services.[4] The United Network of Organ Sharing (UNOS) supports the presence of this professional in multidisciplinary transplant teams. Also, this item is checked in transplant centers accreditation process by Medicare and Medicaid Services. According to the UNOS's guideline the main functions and responsibilities of pharmacists involve: (i) caring of patients after the transplant; (ii) active discussion within the multidisciplinary team to evaluate and if necessary to adapt the medicine regime; (iii) development and implementation of therapeutic protocols; (iv) medication reconciliation; (v) education/orientation/information for patient and team concerning the pharmacotherapy; (vi) monitoring the use of the medicines; (v) development of strategies for cost reduction.[5]

The majority of complications associated to treatment of patients after transplants are associated to the immunosuppression. Among the reasons, the non-adherence to treatment and adverse reactions are the most relevant. Failing in keeping immunosuppression under control can lead to debilitating disease and ultimately allograph failure.[6]

Systematic enrolment of pharmacists in multidisciplinary kidney transplant teams has been associated with positive outcome. In 2001, Chisholm ***et al.***, identified better results in the treatment adherence for immunosuppressant for the groups under pharmaceutical care (96.1 ± 4.7% versus 81.6 ± 11.5%, p <0.001). In a second study, clinical pharmacy services showed a positive impact in managing the blood pressure in Afro-American patients after kidney transplantation.[7] In 2009, a one-year long prospective randomized study conducted by Klein ***et al.*** found out that the treatment adherence in the intervention group was significantly superior (p<0.015).[8] Musgrave ***et al.*** (2013) reported that the enrollment of pharmacist in the process of medication reconciliation significantly reduced prescription errors, increasing the safety in those patients after solid organ transplant.[9] In this context, the goal of this study was to describe pharmaceutical interventions performed in a Brazilian tertiary hospital to improve treatment outcomes of patients underwent kidney transplantation.

Methods

The study was previously approved by the ethic committee in research of the hospital Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA) under the protocol number 476.840. The ISCMPA is a complex composed by several hospitals, located in Southern Brazil. It has two kidney transplant ambulatories and 1042 beds; 62 of which are located in the Dom Vicente Scherer Hospital, which is specialized in transplantations. This study was part of a Randomized Clinical Trial (RCT) which objective was to evaluate the contribution of the services provided by a clinical pharmacist in an ambulatory care renal transplant setting.

Patients and data collection

Sixty-four patients participate in this study. All of them performed kidney transplant at Dom Vicente Scherer Hospital between 2013 (December 20th) and 2014 (August 19th). The inclusion criteria were: age ≥18 years and ability to read, understand and sign a free written and informed consent form. The exclusion criteria were: taking part in clinical research with new immunosuppressants, having kidney and a second solid organ transplanted, a transplanted kidney in absence of renal function and patient's death during the transplantation hospitalization.

The follow up of the patients by the clinical pharmacist was done after hospital discharge during a period of 12 months. The frequency of consultations varies according to the group to which the patient was allocated to the RCT (12 months in group 1 and 6 months in group 2).

The pharmacist with previous experience in kidney transplant collected the data during the appointments. The appointments took place Tuesday afternoon at the renal transplant ambulatories.

Pharmaceutical interventions

The pharmaceutical interventions were performed when the clinical pharmacist identify a drug related problem, that is an event that causes or can cause medication-related negative outcomes.[10]. The medication-related negative outcomes are unwanted health alterations due to the use (or interruption) of a medication and can be classified as negative outcomes related to necessity, to effectiveness or to safety. The designation of medication-related negative outcomes followed the Third Consensus of Granada.[11]

The pharmaceutical interventions were classified according as per Riba ***et al.*** (2000). First, in "adequate", "indifferent" or "inadequate"; next, considering the significance.[12]

The scheme of clinical method for pharmaceutical attention to the patient is described below:

1. Interview with the patient (patient profile, clinical background, pharmacotherapeutic history); 2. Revision of the prescription; 3. Review of laboratory exams, including blood levels of immunosuppressants; 4. Identification of drug related problem and medication-related negative outcomes; 5. Pharmaceutical intervention aiming patient or health professional;6. Individual follow up of patient.

The monitoring process was focused mainly on two aspects: a) effectiveness through laboratorial exams and incidence of allograph rejection/failure and, b) safety through immunosuppressant blood levels and by quantifying the most relevant adverse reaction after transplantation (i.e. hepatotoxicity, cytomegalovirus infection, neurotoxicity and post-transplant diabetes mellitus). For the later, diagnosis of post-transplant diabetes mellitus was done after two glucose tests in fasting in different days, considering the value of 126 mg/dL. Hepatotoxicity was defined by increasing of transaminases three times above the reference level. Physician, using clinical criteria, identified neurotoxicity. Infection by cytomegalovirus was defined by the presence of viral component after indirect immunofluorescence.

During the analysis of prescription drugs, the clinical pharmacist performed the medication reconciliation at the hospital discharge. Also, pharmaceutical interventions were performed regarding the relevance of current prescription (e.g. need for new medicine, indication, dose, frequency, time for intake).

Data organization and analysis

The data were analyzed in the SPSS 19.0 program. Descriptive analysis was performed with absolute and relative frequencies, means and standard deviation. Survival analysis was performed using the Kaplan-Meier method to estimate the survival free of acute rejection confirmed by biopsy (effectiveness measure) at the end of 12 months.

Results

Among the 64 patients followed up, 53.1% were male, with a mean age of 46.2 (SD=14.3) years. The demographic data and patient background information, including medical protocols can be seen in Table 1. The average number of medications was 7.91 (SD=1.83) and 8.17 (SD=2.31) right after hospital discharge and 12 months after discharge, respectively.

The pharmacist had an average of 20 minutes (5-30 minutes) for the medication reconciliation at hospital discharge. In the first visit to the kidney transplant ambulatory, the time for each appointment was 30 min per patient (25-40 min). In total, the pharmacist performed 224 pharmaceutical appointments and 226 pharmaceutical interventions (3.25 SD=2.37 per patient), mainly oriented to the patient (70.4%). The most frequent ones were reschedule medicine intake after discharge from hospital and educate patients that skipping doses of medicines or those with post-transplant diabetes mellitus, based on glucose exam. Pharmaceutical interventions oriented to health professionals were related mainly in adjusting doses of medicines, specially, on reducing immunosuppressant's doses (Table 2). All interventions were classified as adequate. Regarding their importance, 115 (50.9%) were significant, 86 (38.1%) very significant and 25 (11.1%) extremely significant.

Table 1. Demographic data and patient background.

Demographics	**N = 64**
Male, n (%)	34 (53.1)
White, n (%)	42 (65.6)
Age, (average of years ±SD)	46.2 ± 14.3
Type of dialysis prior transplantation, n (%)	
Hemodialysis	53 (82.8)
Peritoneal dialysis	4 (6.3)
None	7 (10.9)
Transplant information	
Decease donor, n (%)	48 (75.0)
Age of donor, (average of years ±SD)	42.7 ± 19.5
Previous transplantation, n (%)	13 (20.3)
Leading cause for CKD*, n (%)	
Systemic hypertension	9 (14.1)
Diabetic nephropathy	2 (3.1)
Polycystic kidney disease	8 (12.5)
Primary glomerulonephritis	6 (9.4)
Hereditary glomerulonephritis	5 (7.8)
Secondary glomerulonephritis	1 (1.6)
Neoplasm	1 (1.6)
Reflux nephropathy	5 (7.8)
Obstrutive uropathy	4 (6.3)
Hemolytic-uremic syndrome	1 (1.6)
Unknown	22 (34.4)
Immunological induction therapy, n (%)	
Basiliximab	40 (62.5)
ATG	22 (34.4)
None	2 (3.1)
Initial maintenance therapy, n (%)	
Tacrolimus	62 (96.9)
Mycophenolate sodium	64 (100.0)
Prednisone	64 (100.0)
Cyclosporine A	1 (1.6)
Transplant hospitalization period	
Days at the hospital for transplantation, (average ±SD)	30.3 ± 19.9

*CKS: chronic kidney disease; ATG: antithymocyte globulin.

The monitoring process was focused mainly on two aspects: a) effectiveness through laboratorial exams and incidence of allograph rejection and, b) safety through immunosuppressant blood levels and by quantifying the most relevant adverse reaction after transplantation.

The number of acute rejection confirmed by biopsy was 36 (56.2%). Most acute rejection events (31; 86.1%) happened during hospitalization for the transplantation. Only five (13.9%) took place after the transplantation hospitalization discharge.

The 36 rejection episodes were rated as follows: 15 (41.7%) as expanded criteria and patients received treatment, 19 (52.8%) grade 1 A, 1 (2.8%) grade 2 A and 1 (2.8%) late acute rejection.

An association between late onset renal function and acute rejection episodes, 33 patients had immediate renal function after renal transplantation, 11 from them had an acute rejection episode. Of the 31 patients with delayed graft function, 22 presented an acute rejection episode, p=0.003.

Table 2. Pharmaceutical interventions (Pharmaceutical interventions) performed.

Intervention (patient-oriented)	**n (%)**
Rescheduling medicine intake (reconciliation after discharge from hospital)	64 (28.3)
Education after patient narrative – self-medication	3 (1.3)
Education after patient narrative – alcohol abuse	4 (1.8)
Education after patient narrative – drug abuse	2 (0.9)
Education after glucose exam – patient with post-transplant diabetes mellitus	23 (10.2)
Education due to immunosuppressant dose intake higher than prescribed	3 (1.3)
Education due to immunosuppressant dose intake lower than prescribed	3 (1.3)
Education due to wrong dose intake of other medicine	7 (3.1)
Education after skipping immunosuppressant dose	9 (4.0)
Education after skipping dose of other medicine	25 (11.1)
Education on right time for blood sampling to monitor tacrolimus – after skipping dose	7 (3.1)
Education on insulin usage – patient with post-transplant diabetes mellitus	9 (4.0)
Partial total 1	159 (70.4)
Intervention (health professional-oriented)	**n (%)**
Increasing on immunosuppressant dose	4 (1.8)
Increasing on other medicine dose	1 (0.4)
Identifying need for tuberculosis prophylaxis	8 (3.5)
Reducing of anticoagulant dose	2 (0.9)
Reducing of immunosuppressant dose	25 (11.1)
Reducing of other medicines	3 (1.3)
Register of moderate drug interaction	3 (1.3)
Requesting for blood/urine test	8 (3.5)
Suggesting drug prescription	13 (5.6)
Partial total 2	67 (29.6)
Total	226 (100.0)

Six patients had graft loss and three of them died. A patient had renal graft loss four months after transplantation due to non-adherence to treatment and three months after returning to hemodialysis, he died at home, from unknown causes. This patient was a chronic user of illegal drugs; it was discovered after transplantation. The second patient, with diabetes, was hospitalized four times after transplantation with severe diabetes complications, with the amputation of both lower limbs followed by severe infectious disease and died 11 months after transplantation. The third dead patient had low adherence to the immunosuppressive treatment and died 8 months after transplantation due to an infectious disease.

Three other patients experienced renal graft loss and were alive, undergoing dialysis, by the end of the 12-month follow-up period. A patient had interstitial fibrosis and tubular atrophy, leading to renal graft failure 11 months after transplantation. This patient presented nephrotoxicity symptoms due to the immunosuppressants. A second patient had graft loss due to arterial kidney stenosis three months after transplantation and the third due to underlying disease relapse – focal segmental glomerulosclerosis (FSGS).

The free survival of acute rejection was 59.4% in the first month, 53.1% in the third month and 48.3% in 12 months (Figure 1).

The most frequent types of negative outcomes observed were those related to ineffectiveness of the immunosuppressant treatment (Table 3).

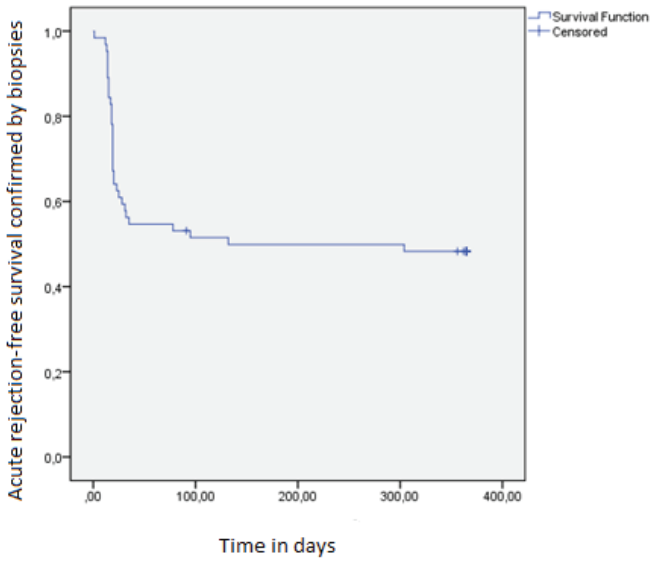
Problems of safety and necessity were expressive too. In relationship to the adverse drug reactions (ADR) with clinical relevance, 23 patients (35.9%) were diagnosed with post-transplant diabetes mellitus, 17 patients with neurotoxicity (26.6%), 14 patients with hepatotoxicity (21.9%) and 38 with cytomegalovirus infection (59.4%). In 13 cases, pharmacist identified the necessity of starting the use

of medicines: antibiotic prophylaxis for dental treatment (3), statins to modify lipid profile (4), insulin/oral antidiabetic to modify glucose levels in diabetic patients (2) treatment with electrolytes (1), for urinary tract infection (1), sleep disorder (1) and postherpetic neuralgia (1).

Table 3. Classification of medication-related negative outcomes (proven or suspected).

Premises of Pharmacotherapy	medication-related negative outcomes	n (%)
Necessity	Health problem not treated	21 (18.4)
	Effect of unnecessary drug	3 (2.6)
Effectiveness	Non-quantitative ineffectiveness	34 (29.8)
	Quantitative ineffectiveness	15 (13.2)
Safety	Non-quantitative unsafe	11 (9.6)
	Quantitative unsafe	30 (26.3)
Total		114 (100.0)

Figure 1. Acute rejection-free survival-12 months of follow-up, n = 64.



Discussion

Our study suggests that pharmaceutical interventions can contribute positively for reduction of medication-related negative outcomes after kidney transplant. Two hundred and twenty-six interventions were done during the appointments (average of 3.25 SD=2.37) of which, almost half (112 interventions - 49.6%) were directed to patient education. The relevance of the clinical pharmacist was based on the number of interventions performed, as well as its significance: 25 (11.1%) were extremely significant. In a study conducted in a post-transplant unit (Georgia, US) 76.4% of pharmaceutical interventions were classified as "significant", being 28.6% related to non-treated medical condition and 26.6% to medicine over dosage.[13] In our study, the most frequent interventions were those associated to reschedule medicine intake (28.3%), dose adjustment of immunosuppressant (12.9%, being 11.1% due to over dosage), and post-transplant diabetes mellitus patients orientation after glucose examination (10.2%). Interventions to improve treatment adherence are also relevant. Non-adherence to treatment is correlated to a progressive deterioration of kidney functional, not rarely associated to acute rejection.[14] It is likely that non-adherent patient relate the chronic non-adhesion to the allograph lost.[15]

An important clinical outcome is the reoccurrence of acute rejection confirmed by biopsy. Most of these events (31 – 86.1%) took place during internment for transplant, where the highest immunological risk is present. The small difference between the free survival of acute rejection for the first (59.4%) and 12th-month after hospital discharge could be linked to the pharmaceutical interventions performed during this period.

Prospective studies investigating the relationship between non-adherence and clinical results are scarce and existing studies use different definitions or different operational measures. It makes harder to reach a consensus on how much non-adherence is sufficient to result in detrimental clinical outcomes. Some data indicate that even small deviations from the prescribed regime (i.e. a maximum of 5% non-adherence to the immunosuppressive regime) are sufficient to generate unfavorable outcomes.[16] It indicates that, in contrast to other chronic diseases, such as dyslipidemia or hypertension, partial adherence (<100%) may not be sufficient to maintain the allograft.

Education on the correct use of the immunosuppressant and other drugs must be a continuous effort, aiming alograph survival. [17, 18]. In many cases the patients also need to combine the transplant treatment to previous existing conditions such as hypertension, diabetis or infecctious disease.[19] Polypharmacy increases the possibility of drug interation and adverse drug reaction. In this study, the average number of medicines at hospital discharge was 7.91(SD= 1.83) and 8.17 (SD=2.31) after 12 months from the transplant.

The maintenance therapy used for 62 patients (96.9%) combined tacrolimus, sodium mycophenolate and prednisone. As blood concentration of tacrolimus can be easily measured, it becomes an important tool in monitoring the effectiveness, adherence and safety of treatment. In all time points, the average level was within the reference values. However, the immunosuppressant concentration reflects an instant picture of the administration and can be influenced the "white coat adherence", in which the patient starts taking the medicine a few days before the medical appointment.[20]

Adjustment of therapeutic dose (either for higher or lower levels) worth to be mentioned as a relevant intervention. In this sense, the most common pharmaceutical interventions was the request for reducing the dosage (25 interventions). Taking tacrolimus as an example, which was used for most of the patients, supratherapeutic doses can induce post-transplant diabetes mellitus, nephrotoxicity and neurotoxicity.

Immunosuppressant's adverse reactions such as post-transplant diabetes mellitus were observed in a retrospective cohort study performed at the same place of this study. The cumulative incidence of post-transplant diabetes mellitus was 24.6% and 17.2% for patients using tacrolimus or cyclosporine, respectively.[21] In the present study, the incidence of post-transplant diabetes mellitus (36%) was higher than previously observed in the cohort (20.6%). This difference could be explained by the fact that in our study, most patients have received tacrolimus on maintenance therapy (96.9%).

When acting in the ambulatory care the pharmacist should monitor the signs and symptoms related to cytomegalovirus infection and follow the results of the antigenemia. The incidence of cytomegalovirus infection (59.4%) was similar to the frequency observed in a study conducted in Brazil (63.4%) by Requião-Moura, Matos, Pacheco-Silva, 2015.[22] In a previous study with 477 patients after kidney transplant, cytomegalovirus infection was found in 64% and disease in 24% of the patients, being the risk of acute rejection increased 1.6 an 2.5-fold for the infection and the disease, respectively.[23] Researchers from South Korea found independent risk for the allograph survival in patients infected with cytomegalovirus (HR=2.2, p<0.011).[24]

Activities of pharmaceutical care associate the patient education, advising, reviewing of therapy and monitoring the outcomes. Self-medication can generate negative results and should be avoided for this group of patients. In the first visits, three patients were found to self-medicate, which may be related to the educational process. Also, 9 patients (14.1%) confirmed not making use of at least one immunosuppressant (i.e.forgetting), 3 patients were taking a higher dose than prescribed and 3 patients were taking a lower dose (4.7%), which could induce rejection and therefore allograph failure.

The risk of tuberculosis is relevant in developing countries. The frequency of ***Mycobacterium tuberculosis*** infection in those countries varies from 1.2 to 6.4%.[25] Concerning this topic, the relevant pharmaceutical interventions were to suggest to the health team to start tuberculosis prophylaxis and to follow the use of medicines in 8 patients (12.5%). None of these patients developed the disease after the transplant. Because the use of immunosuppressant increases the risk of the disease, isoniazide-based prophylaxis is implemented in patients that are strongly reactants against in the tuberculosis test with purified protein derivative. In a study conducted in Bolivia, researchers found tuberculosis in 2% of the patients who received renal transplant. [26]

The clinical pharmacist must be integrated to the multidisciplinary team, sharing the pharmacological knowledge in order to increase the quality of the assistance to the patients. To provide pharmaceutical care mean the adoption of a work philosophy in which the pharmacist works not only for the patient but with the patient. The actions should be aimed towards the optimization of the therapy, increasing effectiveness and safety of the treatments.

The study presented some limitations: 1. The number of patients is small and the study was conducted in a single transplant center. 2. The study was conducted only in the first year post-transplantation. 3. The results of the interventions come from the practice of the research pharmacist and not from a team.

Other randomized, multicenter clinical trials need to be conducted to evaluate the efficacy of pharmaceutical interventions on hard outcomes, such as allograft rejection and mortality. Economic results must also be measured.

Conclusion

In total, the pharmacist performed 224 pharmaceutical appointments and 226 pharmaceutical interventions (3.25 per patient), mainly oriented to the patient (70.4%) and were considered to be significant (50.9%) or very significant (38.1%).

The most important actions were to suggest the reduction of immunosuppressant doses to the physicians (11.1%) and educate patients with post-transplant diabetes mellitus (10.2%) or those skipping doses of the medicines (11.1%).

The number of acute rejection confirmed by biopsy was 36 (56.2%). Most acute rejection events (31; 86.1%) happened during hospitalization for the transplantation. The small difference between the free survival of acute rejection for the first (59.4%) and 12th-month after hospital discharge could be linked to the pharmaceutical interventions performed during this period.

The clinical pharmacist has an important role in the kidney transplant ambulatory. An active involvement of this professional can increase the quality of the treatment, reducing the risks of medication-related negative outcomes.

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Collaborators:

DG conducted the clinical study, collected data, performed statistical analysis and wrote the article. EK and IH participated in the study planning, data interpretation and carried out a critical review of the article. Everyone is responsible for all job information, ensuring the accuracy and integrity of any part of the work.

Conflicts of interest

The authors declare no potential conflict of interest.

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