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ORIGINAL PAPER

Serum Level of Immunosuppressants as a Marker of Effectiveness of Pharmaceutical Education in Solid Organ Transplantation

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ABSTRACT

Solid organ transplantation promotes an increase in the quality of life of those with diseases that compromise the functioning of a specific organ, maximizing graft survival and reducing the need for retransplantation is essential. Post-transplant medication adherence is one of the factors that influence positive clinical outcomes, with this, the importance of pharmacotherapeutic follow-up at the hospital and outpatient level with the clinical pharmacist is addressed. **Objectives:** To verify the impact of pharmacotherapeutic guidance and follow-up on the compliance of serum levels of calcineurin inhibitors in lung and liver transplant patients. **Methods:** Descriptive and retrospective study with adult liver and lung transplant patients using calcineurin inhibitors, aged over 18 years, between 2018 and 2020. The variation index was calculated through the mean and standard deviation of serum levels collected during the index hospitalization, being used to assess the adequacy of serum levels in three different periods. **Results:** A total of 84 patients were transplanted, including 64 patients (45 liver transplants and 19 lung transplants). In a subgroup analysis, 42.22% of the liver patients and 47.37% of the lung transplant recipients did not have the same serum level in the first post-discharge consultation. After 1 year of transplantation and differentiated outpatient follow-ups, the target serum levels were reached in 63.16% and 77.78% of the studied populations, respectively. **Conclusion:** The importance of clinical action was demonstrated from the reflection obtained on the adequacy and conformity of serum levels of calcineurin inhibitors, not only at the hospital level but mainly on the pharmacotherapeutic follow-up carried out on an outpatient basis, in which we observed a more expressive value.

Descriptors: Liver Transplant; Lung Transplant; Adherence to Medication; Immunosuppression Therapy; Pharmaceutical Attention.

Nível Sérico dos Imunossupressores como Marcador de Efetividade da Educação Farmacêutica no Transplante de Órgãos Sólidos

RESUMO

Os indivíduos acometidos por doenças graves que comprometem algum órgão específico, muitas vezes, necessitam do transplante de órgãos sólidos. A terapia imunossupressora e a adesão ao tratamento medicamentoso influenciam nos desfechos clínicos positivos, como aumento da sobrevida do enxerto e melhora na qualidade de vida. Diante disso, a atuação do farmacêutico clínico a nível hospitalar e ambulatorial mediante acompanhamento farmacoterapêutico propicia a otimização do tratamento pós-transplante. **Objetivos:** Avaliar o reflexo da educação farmacêutica, bem como o acompanhamento farmacoterapêutico na adequação do nível sérico dos inibidores de calcineurina em pacientes receptores de órgãos sólidos. **Métodos:** Estudo descritivo e retrospectivo com pacientes adultos transplantados hepático e pulmonar em uso de inibidores de calcineurina. O índice de variação foi utilizado para avaliar a adequação do nível sérico em três períodos distintos. **Resultados:** Foram incluídos 64 pacientes no estudo, sendo 45 transplantes hepáticos e 19 pulmonares. Em análise de subgrupo, cerca de 50% da população não apresentou conformidade do nível sérico na primeira consulta pós-alta. Após um ano do procedimento cirúrgico e dos diferentes acompanhamentos ambulatoriais, o nível sérico alvo alcançou 63,16% no transplante hepático e 77,78% no transplante pulmonar. **Conclusão:** A importância da atuação do farmacêutico clínico baseia-se no reflexo obtido na adequação e conformidade dos níveis séricos dos inibidores de calcineurina, de forma não exclusiva aos dados iniciais avaliados no hospital no período imediato, mas principalmente no seguimento farmacoterapêutico realizado de modo ambulatorial, em que observamos um valor mais expressivo.

Descritores: Transplante de Fígado; Transplante de Pulmão; Adesão à Medicação; Terapia de Imunossupressão; Atenção Farmacêutica.

INTRODUCTION

Since the 1980s, solid organ transplantation (SOT) has evolved into a safe and effective therapeutic alternative for patients with a significant worsening of their clinical condition or advanced-stage organ failure.[1,2,3] The development of scientific and technical procedures associated with the emergence of new pharmacological options were determining factors for the success of SOT.[4] During its rise, organ donation and transplantation provided society with a new possibility of returning to their daily activities through improvement in quality of life and increased survival of those with diseases that compromise the functioning of a specific organ.[5]

Challenges in accessing transplant services within the *SUS* infrastructure and the precarious geographic arrangement of organ supply are leading to an increase in waiting lists.[6] According to the Brazilian Association of Organ Transplants, during the year 2022, the state of Rio Grande do Sul recorded the entry of 261 patients on the list for liver transplantation (LTx), 47 of which died awaiting the procedure; while lung transplantation (LuTx) had an increase of 48 people, with 17 patients dying while waiting.[7] In view of this, strategies must be developed to prolong graft survival, thus reducing the need for a new surgical procedure. In this way, it is possible to improve the patient's quality of life and impact the waiting time of those waiting for a transplant.[8]

The improvement in post-transplant survival rates has been associated with greater efficacy of immunosuppressive therapy, as well as medication adherence that allows the constancy of the serum level (SL) of Tacrolimus (TAC) or Cyclosporine (CSA) within the desired therapeutic index. It is possible to reduce or avoid subtherapeutic levels associated with episodes of acute rejection up to graft loss and supratherapeutic levels related to neurotoxicity, cardiovascular events and acute renal failure.[9,10,11,12]

In order to improve medication adherence and minimize fluctuations in serum levels, pharmacotherapeutic monitoring is an essential strategy.[13] Poor adherence to medication is a prevalent issue, with estimates ranging from 20% to 50%. This can lead to a three times greater risk of late acute rejection and a seven times greater risk of graft failure.[14]. However, measuring the impact of the effectiveness of pharmaceutical intervention is a challenge. At the time of discharge, variables influence the patients' and their support network's understanding of the guidelines regarding their therapeutic plans, such as the diversity of information provided by the professionals accompanying them, post-surgical stress, cognitive capacity, and psychological. Therefore, the study aims as a primary outcome to evaluate the impact of education and post-discharge pharmaceutical monitoring on the adequacy of the serum level of calcineurin inhibitors in lung and liver transplant patients in the first post-discharge consultation, on the thirtieth-day post-discharge and one-year post-transplant.

METHOD

Study design

This study is a descriptive and retrospective analysis that was conducted at a university hospital in Porto Alegre. The study focused on adult patients who had undergone liver and lung transplant surgeries between 2018 and 2020..

Population

Patients aged 18 years or older, liver and lung transplant recipients using calcineurin inhibitors (CNIs) – Tacrolimus(TAC) or Cyclosporine(CsA); those with readmissions before completing 30 days post-transplant, patients transplanted from other organs and those who died during the index hospitalization were excluded. Data were collected and stratified during the months of August to December 2021.

Pharmaceutical education is part of the routine of the clinical pharmacy service and is carried out in the index hospitalization with all patients receiving solid organs. Upon discharge, patients are guided with educational materials and tables with the dosage schedule to improve adherence to medication treatment. Lung transplant patients receive pharmacotherapeutic follow-ups in the outpatient clinic with a multidisciplinary team (medical team, pharmacist, and nurse), while liver transplant patients receive outpatient follow-ups only with the medical team.

Sample size

The collection covered data from 84 patients, 59 of whom had liver transplants and 25 lung transplants. Subsequently, stratification and evaluation were carried out according to the inclusion and exclusion criteria, ultimately comprising a convenience sample of 64 recipients (45 liver and 19 lung transplant recipients).

Variables

The variables were obtained exclusively through direct analysis of electronic medical records. From this, the following parameters were evaluated: demographic data (sex, date of birth and education), underlying disease (indication for the transplant), date of

transplant, serum TAC/CsA level values during hospitalization, at the first consultation outpatient post-discharge, 30 days post-discharge and one year after transplant. Polypharmacy and concomitant use of medications that induce or inhibit CYP3A4 were assessed through discharge prescription.

Bias

One of the main limitations of the study is the sample size. Due to the context of monitoring post-transplant patients, a bias may be considered for analyzes with statistical correlation tests between groups. Therefore, it was decided to analyze the data in a descriptive way in a convenience sample of both groups.

Furthermore, the individualization of clinical assessments regarding the definition of the target serum level of immunosuppression for each patient stands out as a potential bias observed during the study, due to the difficulty in establishing general standards of control and adaptation of immunosuppression.

Therefore, it was necessary to use the serum level variation index for each patient as a parameter to assess compliance throughout post-discharge follow-up. Thus, intrapatient variability associated with non-modifiable and poorly modifiable determinants, considered sources of bias at the serum level, was minimized.

In order to mitigate selection bias and reduce errors in information collection, data was double checked, stratified by different pharmacists.

Statistical methods

The collected data were stored in an electronic database using Microsoft Excel® software and descriptive analysis was carried out using the Statistical Package for the Social Science (SPSS) version 18.0.

Categorical variables, such as age, sex, education, and reason for LTx and LuTx, were presented in absolute (n) and relative frequency (%). The number of days hospitalized, medications at hospital discharge and the serum level variation index were calculated using the mean and standard deviation of the serum levels collected during each patient's index hospitalization. Serum level compliance at the first outpatient consultation and on the thirtieth-day post-discharge was analyzed based on the individual variation index for each patient, considering values within the standard deviation.

Furthermore, medications were considered to interfere with the serum level of CIN when used concomitantly with medications that induce or inhibit CYP3A4, namely: Rifampicin, Isoniazid, Amlodipine, azole derivatives and Carbamazepine. The descriptive analysis of this data was presented in absolute (n) and relative frequency (%).

Ethical aspects

The university hospital's Health Research and Ethics Committee approved the project under identification 2021-0507. Data were collected after approval, following the Brazilian General Data Protection Law. Waiver of the Free and Informed Consent Form was authorized as it used only anonymous databases with computerized records collection. The authors declare that they have no conflict of interest.

RESULTS

During the study period, 84 patients were transplanted, 59 liver and 25 lung transplanted. Of these, 64 patients (45 liver and 19 lung transplants) were included due to compliance with the inclusion and exclusion criteria. The demographic characteristics of the population are detailed in Table 1, below.

The adequacy regarding the serum CNI level of both groups is represented according to the SL compliance in the 1st outpatient consultation, 30 days post-discharge and 1-year post-transplant, the average hospitalization, the number of medications at discharge and the concomitant use of interfering medications are described in Table 2.

In an attempt to evaluate the influence of outpatient follow-up, a descriptive analysis was carried out in the subgroup of those patients who did not have compliant serum levels at the first post-discharge consultation. The SL of the non-compliant population at the first consultation was analyzed one year after transplantation, with the results shown in Table 3.

To analyze the influence of the concomitant use of medications that induce or inhibit CYP3A4, the mean SL of patients was taken at the time of discharge, 30 days post-discharge and one-year post-transplant. The data are presented in Table 4.

Table 1. Demographic characteristics of liver and lung transplant patients (*Hospital de Clínicas de Porto Alegre, RS* August to December 2021).

	Liver transplant		Lung transplant	
	n	Frequency (%)	n	Frequency (%)
Age (years)				
18 – 30	5	11.11	5	26.32
31 – 50	11	24.44	2	10.53
> 51	29	64.45	12	63.15
Sex				
Female	22	48.89	7	36.85
Male	23	51.11	12	63.15
Education				
Illiterate	1	2.22	-	-
Incomplete 1st degree	14	31.11	8	42.10
1st degree complete	5	11.11	3	15.79
Incomplete 2nd degree	3	6.67	-	-
complete 2nd degree	11	24.44	5	26.32
Superior	10	22.22	3	15.79
Reason for LTx	n	Frequency (%)		
HCV cirrhosis + HCC	18	40.00		
HBV cirrhosis + HCC	2	4.44		
NAFLD cirrhosis	8	17.9		
PSC cirrhosis	4	8.89		
Alcohol cirrhosis	2	4.44		
Severe acute liver failure	5	11.11		
Others	6	13.33		
Reason for LuTx			n	Frequency (%)
COPD			8	42.11
Idiopathic pulmonary fibrosis			5	26.31
Cystic fibrosis			3	15.79
Others			3	15.79

LTx (Liver Transplant); HCV (Hepatitis C Virus); HBV (Hepatitis B Virus); HCC (Hepatocellular Carcinoma); NAFLD (Non-Alcoholic Fatty Liver Disease); PSC (Primary sclerosing cholangitis); LuTx (Lung Transplant); COPD (Chronic obstructive pulmonary disease).

Table 2. Description of the parameters evaluated in the population (Hospital de Clínicas de Porto Alegre, RS – August to December 2021).

	Liver transplant		Lung transplant	
		Mean ± SD		Mean ± SD
Hospitalization (days)		20.50 ± 20.54		22.50 ± 22.06
Medicines in medical release		7.00 ± 2.59		8.50 ± 2.96
	n	Frequency (%)	n	Frequency (%)
Concomitant use of interfering medications	25	55.56	6	31.58
SL Compliance: 1st outpatient consultation	26	57.78	9	47.37
SL Compliance: 30 days post-discharge	23	51.11	8	42.11
SL Compliance: 1 year post-transplant	20	44.44	12	63.16

SD (Standard Deviation); SL (Serum level).

Table 3. Adequacy of SL after 1 year in the non-compliant subgroup in the 1st post-discharge consultation (Hospital de Clínicas de Porto Alegre, RS – August to December 2021).

	1st consultation post-discharge		1 year post-transplant	
	n	SL non-compliant (%)	n	SL on target(%)
Liver transplant	19	42.22%	12	63.16%
Lung transplant	9	47.37%	7	77.78%

SL (Serum level).

Table 4. Average serum level of transplant patients at 3 moments (discharge, 30 days post-discharge and 1 year post-transplant) (Hospital de Clínicas de Porto Alegre, RS – August to December 2021).

	Average serum level			
	Medications interfering with discharge (%)	Discharge	30 days post-discharge	1 year post-transplant
Liver transplant	55.56%	6.85	8.20	6.35
Lung transplant	31.58%	8.10	8.35	7.75

DISCUSSION

According to European clinical guidelines, fluctuations in serum levels of immunosuppressants, whether due to poor adherence, genetic or clinical factors, have an important impact on the negative outcomes associated with transplantation, especially in the first months. Such intrapatient variability may be associated with non-modifiable determinants, such as genetic factors, associated with polymorphisms in CYP3A4. In addition to factors that are not very modifiable, such as clinical factors related to hypoalbuminemia, renal failure, and anemia, among others, it is crucial to highlight poor adherence, which is a modifiable factor and can be addressed and prevented in collaboration with the healthcare team.[15]

Among the factors related to the serum variation of the immunosuppressant, the large number of drug interactions stand out, in particular, the change in the pharmacokinetics of calcineurin inhibitors caused by CYP3A4 inhibitors or inducers, as they are substrates of the enzyme, which can cause subtherapeutic levels or supratherapeutic drugs, directly influencing graft function.[16] In the present study, at the time of discharge, we identified the concomitant use of CYP3A4 inhibitor medications (Amlodipine and azole derivatives) in liver transplantation, around 56%, and in lung transplantation, around 32%. Even though this potential drug interaction could lead to overestimated values at discharge, it was observed that serum levels were lower when compared to data from the thirtieth-day post-discharge and one-year post-transplant, as shown in Table 4, proving the window opportunity to optimize therapy with the follow-up of these patients. The significant use in liver transplant patients, when compared to lung transplant, may be related to comorbidities prior to transplant, such as high blood pressure and the need for therapeutic replacement of the antihypertensive drug in accordance with the post-transplant clinic. The use of azole derivatives is carried out with different approaches in different transplants. In cases of liver transplantation with multiple abdominal interventions in the postoperative period, the use of Fluconazole is suggested if intra-abdominal infection is suspected. In lung transplantation, the use of Voriconazole is part of the aspergillosis prophylaxis protocol for patients at risk. In some special situations, Fluconazole can be used as an intentional interaction strategy for those with difficulty achieving the desired therapeutic range.

Individuals with certain sociodemographic characteristics are considered to be the most vulnerable and susceptible to non-adherence. This includes adolescent and elderly patients, those with a lack of social support, a low level of education, a low family income, and those with a busy lifestyle.[15,17] Among the parameters evaluated, the study identified a high prevalence of patients with incomplete primary education in both groups of patients and a predominance of a population over 51 years of age. Understanding these data becomes important in the context of evaluating modifiable versus non-modifiable factors related to the compliance of serum levels of calcineurin inhibitors in LTx and LuTx patients.

It is known that liver and lung diseases included as an indication for transplantation affect individuals of different ages. According to the literature, there is a predominance of male transplant patients aged over 50 years, regardless of the type of organ transplanted, liver or lung.[18,19] In this analysis, a prevalence of liver transplant patients above 51 years old, with cirrhosis caused by the Hepatitis C virus being the main underlying disease. This data could be justified by the innovation in the pharmacological treatment of HCV, as well as the investment in access to universal treatment for carriers, resulting in an extension of the quality of life of these patients. However, this advantage may not be reflected in the LuTx group due to the prolonged waiting time on the transplant list, worsening clinical conditions and challenges in managing more serious lung diseases. This, together with difficulties in accessing and correctly using inhalation devices, may justify a later lung transplant.

Immunosuppression is one of the main pillars in post-transplant patients. However, the complexity of pharmacotherapy, the long duration of treatment, the number of new medications in the routine and the multiple dosage schedules become factors that interfere with treatment adherence. Polypharmacy is frequent in this patient profile because, in addition to immunosuppressants which aim to prevent organ rejection, it is necessary to use medications to prevent and treat comorbidities acquired before or after transplantation.[15,20] Asavakarn *et al*, in a prospective study, they determined the average number of medications used by liver transplant patients during the period from 2012 to 2014, in which it was identified that the majority had around 8.55 (SD=3.5) medications at the time of discharge.[21] This data reinforced the importance of teaching by the multidisciplinary team, and the result was evaluated through the reduction in medication-related problems. Similarly, this study showed that the LTx group had approximately seven medications at the time of discharge, while the LuTX group had approximately nine medications. The data indicates that liver and lung transplant patients receive similar treatment as recommended by other transplant centers. Post-LuTx patients have a more robust pharmacotherapy due to greater immunosuppression and continuity of pre-existing pharmacological therapies. For instance, individuals who have undergone transplantation for cystic fibrosis may require continued pharmacotherapy to manage comorbidities associated with the underlying disease, such as exocrine pancreatic insufficiency, among other conditions.

Studies demonstrate that non-adherence to pharmacotherapy is related to the high incidence of late acute rejection and graft loss.[10,12] In adult liver transplant patients, reported rates of non-adherence vary from 15% to 40%.[21] In patients adults with lung

transplants, a systematic review showed rates ranging from 2.3% to 72.2%.[22] Therefore, assistance involving a multidisciplinary team is a key strategy to reduce non-adherence rates.

It is already established that the involvement of clinical pharmacists in the care of transplant patients can help improve adherence to treatment.[23] They provide detailed information about each medication, promote patient and family education, and help plan the patient's daily routine.[21] A study by Duwez *et al.* shows that repeated education during the first year post-transplant can positively impact patients' understanding and mastery of their treatment.[24] Given the importance of patient education and the appropriate use of medications post-solid organ transplantation, this study aims to verify the impact of pharmacotherapeutic guidance and follow-up on compliance with the serum level of calcineurin inhibitors. This is because there is a well-established relationship between adherence and SL variability.

Thus, when evaluating the compliance of the serum level at the first outpatient consultation, only half of the patients had adequate therapeutic target immunosuppression, as shown in Table 2. This data suggests that, at the time of discharge, variables such as the considerable amount of information provided by different professionals, post-surgical stress and cognitive and psychological skills can affect the understanding of initial care after transplantation. This highlights, once again, the importance of monitoring and continued education.

Schuh *et al*, in a study published in 2018 with a population similar to the present case series, demonstrated that 79.7% of post-liver transplant patients showed increased therapeutic levels of Tacrolimus after consultation with a pharmacist.[23] In line with this data, another study that addressed the topic suggested that serum levels of immunosuppressive medications are more likely to be achieved in patients who receive the assistance of a clinical pharmacist on their transplant team. In line with this data, another study that addressed the topic suggested that serum levels of immunosuppressive medications are more likely to be achieved in patients who receive assistance from a clinical pharmacist on their transplant team.[25] In an attempt to highlight this trend in this study, as shown in Table 3, the adequacy of the serum level at the first post-discharge visit was similar in the LTx and LuTx groups. This data can be justified by the equity in the intra-hospital pharmaceutical care provided and the influence of the factors previously mentioned that compromise the understanding of the information at discharge. On the other hand, after one year of outpatient follow-up, it was observed that the LuTx subgroup, which received specialized pharmacotherapeutic follow-up with the clinical pharmacist, showed a significant increase in serum level values within the target therapeutic window. This data reinforces the importance of pharmaceutical work with the multidisciplinary team in the search to promote less variability in serum levels of immunosuppressants and, consequently, better clinical outcomes.

One thing worth noting is that the groups had a relatively small number of patients, which could limit the generalizability of the findings. Additionally, the outpatient follow-up procedures varied between the groups after the patients were discharged, which may have impacted the results. Furthermore, as this was a retrospective study, it was impossible to apply qualitative tools that assessed medication adherence in the population monitored on an outpatient basis by a pharmacist so that the analysis could become more robust. Despite this, the results of this work reinforce the importance of multidisciplinary action in solid organ transplantation, mainly the contribution of the clinical pharmacist in adapting the serum level within the target parameters in the patient's understanding of the proposed treatment and, therefore, in adherence to the pharmacotherapy.

CONCLUSION

Adherence to medication treatment increases patients' quality of life by receiving solid organs by preventing negative clinical outcomes. The role of the clinical pharmacist within the multidisciplinary team is growing and standing out every day, allowing better optimization of pharmacotherapy for patients and greater knowledge and understanding about their own treatment. Based on this, this study demonstrated the importance of this clinical action by presenting the reflection obtained on the adequacy and compliance of serum levels of calcineurin inhibitors. This is not only at the hospital level but also, and just as crucially, in outpatient pharmacotherapeutic monitoring, where we observe a more significant value in compliance, especially in long-term monitoring. The importance of further studies in the area is highlighted, in association with other quantitative and qualitative tools, for a more comprehensive analysis of the correlation between serum level, medication adherence and pharmaceutical education.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Luz TV, Alves PH; Muneretto CS; **Conception and design:** Luz TV, Alves PH; **Data analysis and interpretation:** Luz TV, Alves PH; **Article writing:** Luz TV; **Critical revision:** Luz TV, Alves PH; **Final approval:** Luz TV.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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