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ORIGINAL ARTICLE

Renal insufficiency, mortality, and drug management in heart transplant. Results of the CARIN study

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Summary

Renal insufficiency (RI) is a frequent complication in heart transplant (HT) patients. The main objectives of the Cardiac trAnsplantation and Renal INsufficiency (CARIN) study were to follow the evolution of renal function after heart transplantation (HTx), to identify the factors associated with the decline of renal function, to describe the impact of RI on mortality during 3 years after the HT, and to observe the renal profile of the prescriptions. CARIN was a French retrospective, multicentric, study. Data were collected for patients who received a HT between 2000 and 2005. Data collection was performed at five time points: before HTx (T0), 1(T1), 6(T6), 12 (T12), and 36 (T36) months after HTx. Glomerular filtration rate (GFR) was estimated with aMDRD formula. RI was defined as GFR < 60 ml/min/1.73 m². Four hundred and forty-one patients from five HT centers were included. The prevalences of RI were 28.8% (T0), 54.0% (T1), 50.4% (T6), 51.6% (T12), and 59.6% (T36). Age and cyclosporine were independently linked to the decline of renal function. Hypertension and GFR < 60 at T0 were independent risk factors of mortality. 48.7–64.7% of the nonimmunosuppressive prescriptions were drugs that required dosage adjustment in RI patients or for which no data were available concerning administration in RI patients. RI is highly frequent after HTx. Because RI is a risk factor of mortality, any sparing renal strategies have to be undertaken.

Introduction

Chronic kidney disease (CKD) is an important and a frequent complication after heart transplantation (HTx) [1–11]. As longevity of all solid organ recipients has improved, CKD has become an increasingly prevalent complication in this population. Indeed, in heart transplant (HT) patients, 10–40% have a renal insufficiency (RI) at 3–7 years [1,8,11,12] according to the definition of RI and 5–20% have to undergo dialysis at 9–10 years [4].

Renal impairment has been mostly attributed to the use of calcineurin inhibitors (CNI)-based immunosuppressive regimen, and more specifically to cyclosporine [4,6]. CNI have improved the survival of kidney, heart, and liver transplants [5,13]. Therefore, use of cyclosporine has been widely increased to prevent transplant rejection despite the kidney toxicity.

Indeed, renal failure after HTx is associated with significant mortality and morbidity [1,5,8,14]. Ojo *et al.* [1] reported among HT patients, a higher mortality in dialysis

patients than in nondialysis patients (56.2% vs. 35.9%, respectively). On the other hand, among dialysis patients, mortality of HT patients was greater than in nontransplant patients (56.2% vs. 41.8%) [2]. However, there are no data on the renal profile of the drugs used in this population. In fact, drug handling in RI patients is crucial, because of the pharmacokinetic parameters' modifications and its consequences. For example, Breton *et al.* [15] reported a significant hazard ratio of 1.4, for a 6-year mortality period, related to the exposure to the risk of inappropriate drug use in elderly (≥65 years) RI patients.

The main objective of the Cardiac trAnsplantation and Renal INsufficiency (CARIN) study was to follow the evolution of renal function in French HT patients. The second objective of the CARIN study was to identify the factors associated with the decline of renal function among the HT patients and to describe the impact of RI on mortality during a follow-up period of 3 years after the HTx. Finally, the last objective was to describe the renal profile of the nonimmunosuppressive drugs used in these patients.

Methods

Patients, design, data collected, and definition

Cardiac trAnsplantation and Renal INsufficiency (CARIN) was a retrospective, multicentric, observational study. All HT patients transplanted between 2000 and 2005 in the five participating hospitals were included. We excluded: patients aged <18 years, patients with previous history of renal replacement therapy or kidney transplantation and patients with previous history of HTx. Data collection was performed at 5 time points: before HTx (T0), 1 (T1), 6 (T6), 12(T12), and 36 (T36) months after HTx. Therefore, patients were observed up to 36 months after HTx. Baseline demographic (gender and age), clinical characteristics (weight, height, BMI, hemoglobin, indication for HTx), serum creatinine (SCr), medical history (hypertension, diabetes mellitus), immunosuppressive regimen (drugs, doses, and trough serum levels), and all other drugs were recorded from the medical files of the patients at each time point.

The major endpoints of the CARIN Study were:

1 To describe the renal function of the HT patients

The prevalences of glomerular filtration rate (GFR) < 60 ml/min/1.73 m² at each of the five periods (T0, T2, T6, T12, T36) were described, and patients were classified according to the Kidney Disease Outcomes Quality Initiative/Kidney Disease: Improving Global Outcomes (K/DOQI-KDIGO) classification. Renal function was estimated according to the aMDRD (abbreviated Modification of Diet in Renal Disease) formula [16]:

$$\mathrm{GFR\,(ml/\,min\,/1.73\,m^2)} = 186 \times \mathrm{SCr}^{-1.154} \times \mathrm{Age}^{-0.203} \times 0.742\,\mathrm{(if\ female)}$$

Indeed, it has been shown that the aMDRD formula was significantly better than Cockcroft-Gault (CG) formula [17] for GFR estimation in HT patients [18].

2 To describe the immunosuppressive drugs prescribed

The immunosuppressive drugs prescribed were described (name of the drugs, doses...). Because these drugs were specific to HT patients, they were analyzed separately from other medications.

3 To identity risk factors linked with the decline of renal function and those linked with mortality

Univariate and multivariate analysis were used to identify risk factors associated with the RI (GFR < 60 ml/min/1.73 m²) during the follow-up period. Survival analyses were performed for a 3-year period of follow-up after the HTx.

4 To describe the nonimmunosuppressive medications of the patients

With regard to the medications prescribed to CARIN patients, the drugs that required dosage adjustment were identified in accordance with their pharmacokinetics and available recommendations from two specific reference books and one website on drug dosage adjustment in RI patients:

1. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, fifth edition (Aronoff *et al.*, 2007).
2. The collection: Prescription Medications Guide for Patients with Renal Insufficiency published by the Service ICAR from the Nephrology Department of Pitie-Salpetriere Hospital in Paris, France.
3. The SiteGPR® website (\www.sitegpr.com) founded and managed by Service ICAR. The SiteGPR® is Health on the Net (HON) certified.

Then, medications were classified as "yes" when dosage adjustment was required, "no" when dosage adjustment was not required, and "No Data" when no data were available in the international literature about the dosage adjustment in RI patients. Some drugs were also contra-indicated (CI) in case of RI.

Statistical method

Statistical analyses were performed to describe risk factors of RI and mortality.

1. Renal impairment: univariate analyses were used to compare the data between patients with RI and patients without. For these analyses, the Mann–Whitney U-test and Student's t-test were used to compare continuous data. The

chi-square and Fischer's exact tests were performed to compare categorical variables. A multivariate analysis (logistic regression) was performed, focusing on the factors associated with the decline of renal function. Age, BMI, gender, indications of HT, arterial hypertension at T0, diabetes at T0, GFR at T0, cyclosporine, tacrolimus, and mycophenolate mofetil (MMF) prescriptions were used in the model.

2. Survival analysis: univariate Log-Rank tests were performed to analyze the impact of RI on the survival of HT patients. The multivariate Cox regression was performed to identify risk factors of mortality in HT patients. Age, BMI, gender, indications of HT, arterial hypertension at T0, diabetes at T0, RI at T0 were the parameters used in the Cox model. A *P*-value lower than 0.05 was considered statistically significant. All the analyses were performed with SAS statistical software, version 8.02 (SAS, Inc., Cary, NC, USA).

Results

Description of the population

Four hundred and forty-one HT patients from five centers were included in the CARIN study. Eighty-five patients died during the follow-up period. Table 1 shows the baseline characteristics of the study population before transplantation. Hypertension was reported in 23.8% (T1), 31.9% (T6), 35.0% (T12), and 38.8% (T36). Diabetes was reported in 12.4% (T1), 14.2% (T6), 15.3% (T12), and 16.9% (T36). Finally, means hemoglobin were 11.1 (T1), 12.5 (T6), 12.8(T12), and 13.4 g/dl (T36).

Table 1. Baseline demographic, clinical, and biological characteristics of HT CARIN patients (n = 441).

Patients characteristics	Mean ± SD or percent
Age	47.0 ± 13.1 years
Male (%)	76.4
BMI	23.7 ± 4.0 kg/m²
Etiology of heart disease (%)	
Dilated cardiomyopathy	54.0
Ischemic cardiomyopathy	32.4
Valvular cardiomyopathy	3.6
Congenital heart disease	2.0
Restrictive cardiomyopathy	1.1
Chemotherapy-induced cardiomyopathy	0.9
Other	6.0
Diabetes (%)	9.3
Hypertension (%)	13.6
Hemoglobin	12.9 ± 1.4 g/dl
Serum creatinine	102.2 ± 31.2 µM
GFR < 90 ml/min/1.73 m² (%)	74.2
GFR < 60 ml/min/1.73 m² (%)	28.8

BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation.

Renal function

The mean baseline GFR for the cohort (n = 441) was 75.9 ml/min/1.73 m^2. After T0, a decrease of 15.2%, 13.8%, 16.3%, and 19.3% of the baseline GFR were observed for each time point, respectively.

Renal insufficiency was observed in 28.8% of the patients at T0. The prevalences of RI were 54.0% at T1, 50.4% at T6, 51.6% at T12, and 59.6% at T36. Stages of renal function of the population are reported in Table 2.

Immunosuppressive drugs

The main immunosuppressive drugs used were cyclosporine and tacrolimus. The main maintenance immunosuppression drug combinations at each time point included calcineurin inhibitors and MMF (Fig. 1). Doses and blood levels of each drug were available Table 3.

Risk factors of renal insufficiency

Univariate analyses on the global population reported that the decrease of GFR per month was linked to age (P = 0.001) and diabetes (P = 0.04). The multivariate analysis reported that age (P = 0.04) and cyclosporine (P = 0.0001) were linked to the decline of GFR. However, gender, BMI, indications of HTx, hypertension, diabetes, tacrolimus, MMF, and GFR at T0 were not found to be associated with the decline of GFR in the multivariate analysis.

When focusing on the 314 patients with normal renal function (GFR ≥ 60 ml/min/1.73 m²) at baseline, univariate analyses showed that the incidence RI during the follow-up period was linked to age (P < 0.0001), BMI (P = 0.003), cyclosporine exposure (P = 0.0001), and GFR at HTx (P = 0.0001). When performing a multivariate analysis on the same 314 HT patients, age (P = 0.004), cyclosporine exposure (P = 0.0001), and GFR at T0 (P = 0.0002) were identified as risk factors of developing RI in HT patients.

Risk factors of mortality

Univariate analyses showed that RI (P = 0.0008) at the HTx (Fig. 2), arterial hypertension (P = 0.01), and the prescription of cyclosporine (P = 0.03) were linked to mortality in the CARIN population. However, age, gender, BMI, SCr, diabetes, hemoglobin, and main indications of HTx were not identified as risk factors of mortality. According to the Cox regression (multivariate analysis), arterial hypertension (P = 0.02, hazard ratio = 1.94) and GFR < 60 (P = 0.003; hazard ratio = 2.04) at T0 were both independent predictors of mortality among the CARIN population.

Table 2. Renal function by the stage of kidney disease in HT patients.

		After HTx [% (*n*)]			
GFR (ml/min/1.73 m^2)	Before HTx [% (*n*)] *n* = 441	1 month *n* = 387	6 months *n* = 373	12 months *n* = 366	36 months *n* = 356
≥90	25.8 (114)	15.8 (61)	13.9 (52)	9.8 (36)	8.7 (31)
60–89	45.4 (200)	30.2 (117)	35.7 (133)	38.5 (141)	31.7 (113)
30–59	27.7 (122)	45.0 (174)	44.8 (167)	45.6 (167)	53.4 (190)
<30	1.1 (5)	9 (35)	5.6 (21)	6.0 (22)	6.2 (22)

GFR, glomerular filtration rate; HD, hemodialysis; HT, heart transplant; HTx, heart transplantation.

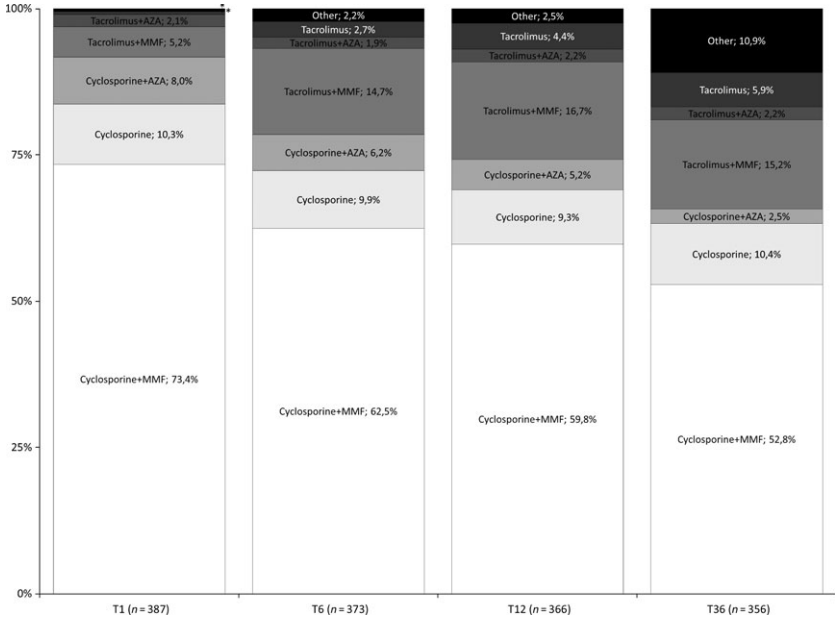

Figure 1 Maintenance immunosuppression drug combinations at time of follow-up. T1: 1 month after heart transplantation; T6: 6 months after heart transplantation; T12: 12 months after transplantation; T36: 36 months after transplantation. *T1, Other: 0.5% **T1, Tacrolimus: 0.5%.

Nonimmunosuppressive medications of the patients

The CARIN patients received 1248 nonimmunosuppressive prescriptions before HTx. Of these 1248 prescriptions, 64.7% were for drugs that required a dosage adjustment in RI patients (labeled "Yes") or for which there were no available data concerning administration in RI patients (labeled "ND"; Fig. 3). Furthermore, 84.1% of the patients received at least one drug that required a dosage adjustment in case of RI (or for which no data were available concerning their administration in RI patients). Only 15.9% of the patients received only drugs that did not required dosage adjustment in case of RI.

After the HTx, the proportion of prescriptions that required dosage adjustments or for which no data were available, decreased, and reached 48.7% at T36 (Fig. 3). Moreover, the percent of patients receiving at least one drug labeled "Yes" or "ND" varied from 96.4% (T1) to 89.1% (T36; Fig. 4). Finally, 3.6% (T1) to 10.9% (T36) of the patients received only drugs for which no dosage adjustment was necessary.

Three hundred and fifty-two different International Nonproprietary Names (INN) were prescribed during the CARIN study. Specific data for the 10 main drugs prescribed were reported Table 4, it included data on pharmacokinetic drug–drug interactions based on two books [19,20].

Discussion

Studies already reported that CKD was common in HT patients, but studies investigating the risk factor of the decline of GFR and of the mortality with univariate/multivariate analyses were not so frequent, especially in France.

This study showed that CKD is a frequent complication after HTx. At 36 months, more than half of the whole population (59.6%) had a RI compared with 28.8% of patients before HTx. Renal dysfunction is common before

Table 3. Prescription, dose, and blood levels of immunosuppressive drugs.

Drugs	1 month after HTx *n* = 387	6 months after HTx *n* = 373	12 months after HTx *n* = 366	36 months after HTx *n* = 356
Cyclosporine				
Prescription (%)	92.3	79.6	75.7	71.6
Dose	268 ± 90 mg	249 ± 75 mg	250 ± 74 mg	182 ± 57 mg
Blood level	251 ± 88 ng/ml	194 ± 62 ng/ml	174 ± 60 ng/ml	123 ± 49 ng/ml
Tacrolimus				
Prescription (%)	7.7	20.1	24.3	27.5
Dose	6.4 ± 3.1 mg	6.3 ± 3.0 mg	5.4 ± 2.4 mg	4.2 ± 2.1 mg
Blood level	12.9 ± 4.5 ng/ml	10.7 ± 4.4 ng/ml	10.7 ± 3.2 ng/ml	8.9 ± 3.1 ng/ml
Everolimus				
Prescription (%)	0.5	1.6	1.9	5.1
Dose	1.0 mg	1.4 mg	1.8 mg	1.7 mg
Sirolimus				
Prescription (%)	–	0.5	–	0.3
Dose	–	1.0 mg	–	2.0 mg
Azathioprine				
Prescription (%)	10.1	8.0	7.4	4.7
Dose	92.9 mg	87.0 mg	86.6 mg	75.0 mg
MMF				
Prescription (%)	78.4	77.7	77.6	71.9
Dose	1818 ± 830 mg	1809 ± 805 mg	1778 ± 778 mg	1919 ± 759 mg
MMS				
Prescription	–	–	0.5	5.6
Dose	–	–	1080 ± 509 mg	1098 ± 460 mg
Steroids				
All steroids (%)	97.7	96.5	95.3	80.6
Prednisolone*	79.8% (24.6 ± 10.2 mg)	79.4% (14.0 ± 6.5 mg)	78.1% (10.0 ± 5.0 mg)	62.6% (6.5 ± 4.9 mg)
Prednisone*	12.4% (13.5 ± 3.0 mg)	13.4% (13.3 ± 3.2 mg)	14.5% (12.0 ± 3.0 mg)	16.3% (8.6 ± 3.2 mg)
Methylprednisolone*	5.2% (21.1 ± 10.0 mg)	3.5% (11.0 ± 7.0 mg)	2.7% (4.0 ± 1.7 mg)	1.1% (4.0 ± 3.5 mg)
Hydrocortisone*	0.3% (–)	0.3% (8.0 mg)	–	0.6% (17.5 ± 3.5 mg)

Dose and blood level: mean ± standard deviation; MMF, mycophenolate mofetil; MMS, mycophenolate sodium; HTx, heart transplantation.
*Percent of prescription (mean dose ± standard deviation).

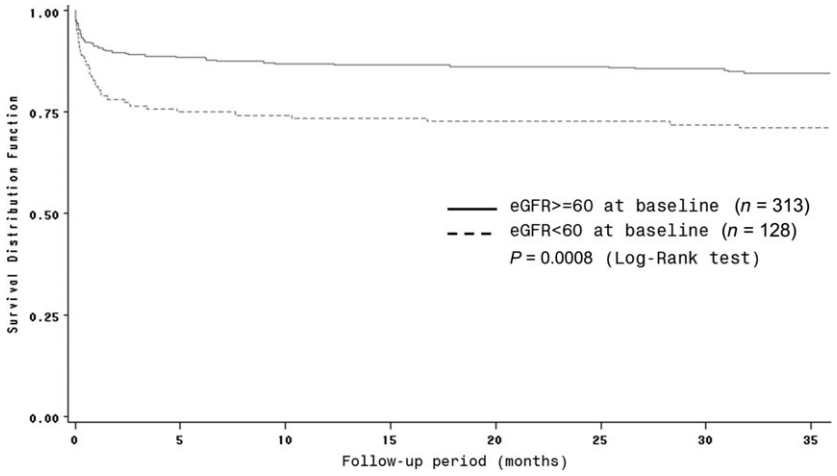

Figure 2 Kaplan–Meyer curves and Log-Rank test in CARIN patients. eGFR, estimated glomerular filtration rate (aMDRD, ml/min/1.73 m²).

HTx, likely due to the hemodynamic effects of pre-existing congestive heart failure, heart failure medicine, and comorbidities such as diabetes mellitus and hypertension [3,6]. After HTx, renal function progressively decreased: patients lost 15–19% of their baseline GFR between 1 and 36 months.

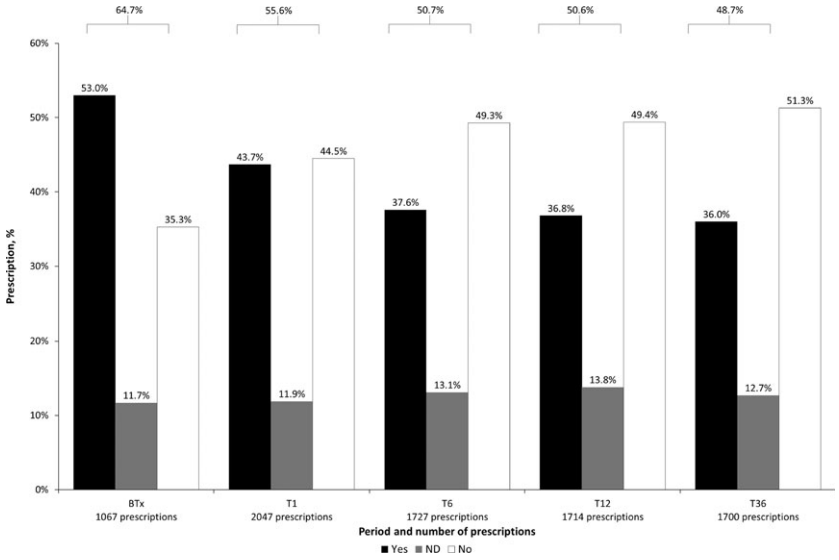

Figure 3 Medication requiring dosage adjustment in renal insufficiency (RI) patients as a percentage of prescriptions. T1: 1 month after heart transplantation; T6: 6 months after heart transplantation; T12: 12 months after transplantation; T36: 36 months after transplantation; BTx, before heat transplantation; Yes, need dosage adjustment in case of RI; ND, no data available concerning administration in RI patients; No, do not need dosage adjustment in case of RI.

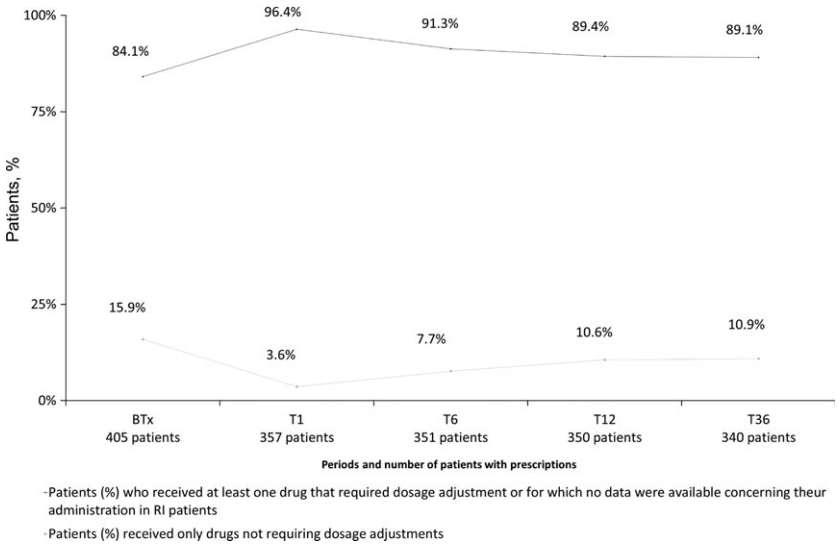

Figure 4 Medication requiring dosage adjustment in RI patients as a percentage of patients. T1: 1 month after heart transplantation; T6: 6 months after heart transplantation; T12: 12 months after transplantation; T36: 36 months after transplantation; BTx, before heat transplantation; Yes, need dosage adjustment in case of RI; ND: no data available about the management in case of RI; No, do not need dosage adjustment in case of RI.

Several studies compared CG and aMDRD for the estimation of GFR [18,21], but besides aMDRD seemed to be better in HT patients, this formula has not yet been clearly validated in this population. Therefore, it is crucial to estimate renal function with at least aMDRD formula in HT patients before and after the HTx.

The prevalence of CKD in HT recipients was high, as showed in our study and in many other [1–6], but the CARIN study had the particularity of presenting univariate and multivariate analyses on the mortality of HT patients. Depending on the type of analysis (univariate or multivariate), a pre-existing RI had an impact on the mortality of HT patients. Interestingly, the curves of the Fig. 2 split in the first few months after HTx and the difference between the two curves remained stable after. Meaning that the increased risk of mortality could be related in time to the

Table 4. Renal profile and pharmacokinetic drug–drug interaction of the 10 main drugs used in the CARIN study.

INN, number of prescriptions	Drug dosage adaptations	PK drug–drug interactions with calcineurin inhibitors
Pravastain, *n* = 1044	Yes	Yes *Coadministration with cyclosporine may increase the oral bioavailability of pravastatin*
Omeprazole, *n* = 733	No	Yes *Coadministration with some PPIs may increase the blood concentrations of tacrolimus*
Furosemide, *n* = 597	Yes	No PK interaction
Acetylsalicylic Acid, *n* = 384	Yes	No PK interaction
Ramipril, *n* = 346	Yes	No PK interaction
Sulfamethoxazole/Trimethoprim, *n* = 345	Yes	Yes *Oral coadministration with cyclosporine may significantly reduce serum cyclosporine concentrations*
Valacyclovir, *n* = 235	Yes	No PK interaction
Insulin, *n* = 183	Yes	No PK interaction
Allopurinol, *n* = 177	Yes	Yes *Concomitant administration of allopurinol may increase cyclosporine blood concentrations.*
Bisoprolol, *n* = 157	Yes	No PK interaction

INN, International Nonproprietary Names; PK: pharmacokinetic; PPI: proton pump inhibitors.

HTx procedure and to the time just after. CKD is well known to be linked to cardiovascular events and cardiovascular death [22]. Therefore, the renal management in such patients is crucial.

Another finding of the CARIN study was the profile of the nonimmunosuppressive drugs used before and after HTx. In fact, a large majority of patients received at least one drug that required a dosage adjustment in case of RI (or for which no data were available for their management in RI patients), and a minority of patients received only drugs that did not require dosage adjustment (Fig. 4). This is crucial because in patients with a reduced GFR, pharmacokinetic parameters of drugs most often are modified.

Not only the urinary route of elimination is impaired but also the other four phases of the pharmacokinetics. First is absorption, which consists of a drug passing from its site of administration into the central compartment: the serum. Next is the second phase, called distribution, during which the drug diffuses into peripheral tissues called compartments, such as the bone, fat, and tissues of the central nervous system. The third phase is metabolism which most often is enzymatic and occurs in the liver, for the major part. RI may influence one or several of these phases, potentially resulting in marked modifications of the pharmacokinetic profile of a drug in RI patients [23,24]. Modifications of the pharmacokinetic parameters of drugs in RI patients expose the patients to a risk of an overdose when the dose is not adjusted appropriately to the patient's renal function. In fact, administering a normal dose of a drug to a patient in whom the elimination processes are impaired exposes the patient to a high risk of overdose-related side effects. Therefore, every patient's prescription should be checked before initiating the treatment and adapted to the level of renal function in order to avoid dose-related side effects.

Some reviews, handbooks, or website (\www.sitegpr.com) provide recommendations on drug management in patients with renal impairment from the stage 1 of chronic renal impairment to the end-stage renal disease [25,26]. Unfortunately, we were not able to analyze the nephrotoxicity of the prescriptions and the cumulative nephrotoxic effect of immunosuppressive regimens.

The CARIN study had some limitations: CARIN was a retrospective "real life" study with no outcome on the efficacy of the immunosuppressive regimens. Therefore, there were no data on rejection. Furthermore, there were no data on the reason of the switch of immunosuppressive drugs. Most of the patients received the same immunosuppressive regimens; therefore, it was not possible to make comparisons. Finally, the induction therapy was not recorded, only the prescription at each time point.

In conclusion, the etiology of CKD in HT patients is multifactorial, but the use of CNI has a major impact on the GFR, as it was found in CARIN patients for the cyclosporine. With a high prevalence of CKD in patients undergoing HTx and the impact of CKD on the survival in this population, it is imperative to undertake monitoring strategies to avoid/minimize long-term renal effects of CNIs. A monitoring of renal function (GFR with aMDRD formula) and the limitation of nephrotoxic drugs exposure (CNI and other) can prevent the degradation of renal function and so improve the life expectancy of HT patients.

Finally, it is important to check the doses of nonimmunosuppressive drugs and to adapt the dose to the level of renal function in order to avoid dose-related side effects.

Authorship

NJ, VL-V, LS, PD, EE, AP, JFO, SP, SV, VP, GD and RG: designed study. NJ: collected data. NJ and LT: analyzed data and wrote the paper. VL-V, LS, PD, EE, AP, JFO, SP, SV, VP, GD and RG: review the paper.

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