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Use of mTOR inhibitors in chronic heart transplant recipients with renal failure: Calcineurin-inhibitors conversion or minimization?

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ABSTRACT

Background: In the last decade, mTOR inhibitors (mTOR-is) have become the cornerstone of the calcineurin inhibitor (CNI)-reduced/free regimens aimed to the preservation of post-transplant renal function. We compared utility and safety of the total replacement of calcineurin inhibitors with a mTOR-i with a strategy based on calcineurin inhibitor minimization and concomitant use of m-TOR-i.
Methods: In a retrospective multi-center cohort of 394 maintenance cardiac recipients with renal failure (GFR < 60 mL/min/1.73 m^2), we compared 235 patients in whom CNI was replaced with a mTOR-i (sirolimus or everolimus) with 159 patients in whom mTOR-is were used to minimize CNIs. A propensity score analysis was carried out to balance between group differences.
Results: Overall, after a median time of 2 years from mTOR-i initiation, between group differences for the evolution of renal function were not observed. In a multivariate adjusted model, improvement of renal function was limited to patients with mTOR-i usage within 5 years after transplantation, particularly with the conversion strategy, and in those patients who could maintain mTOR-i therapy. Significant differences between strategies were not found for mortality, infection and mTOR-i withdrawal due to drug-related adverse events. However, conversion group tended to have a higher acute rejection incidence than the minimization group ($p = 0.07$).
Conclusion: In terms of renal benefits, our results support an earlier use of mTOR-is, irrespective of the strategy. The selection of either a conversion or a CNI minimization protocol should be based on the clinical characteristics of the patients, particularly their rejection risk.

1. Introduction

In the current era of extended survival in heart transplantation, post-transplant renal failure has become a major factor impairing quality of life and with significant prognostic implications. Thus, various renal sparing strategies have been attempted in recent years [1]. As calcineurin inhibitor (CNI) exposure is considered to play a key role in the development of renal damage after cardiac transplantation, most of those strategies have focused on the minimization of CNI therapy. In the last decade, the appearance of mammalian target of rapamycin inhibitors (mTOR-is) (sirolimus and everolimus), a novel immunosuppressant group with apparent lack of intrinsic nephrotoxicity, has emerged as an attractive alternative for this particular purpose.

Initial protocols with de novo use of mTOR-i combined with CNI [2–4] showed a deterioration of renal function unless a significant

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reduction in CNI dosage and serum levels were accomplished [5–7]. This was particularly evident in a recent randomized clinical trial, in which de novo use of everolimus resulted in a significant deterioration of renal function as compared to mycophenolate mofetil unless an importantly reduced cyclosporine trough levels were achieved [8]. In this clinical setting, total avoidance of CNI therapy resulted in an adequate preservation or even improvement of renal function but at the cost of an elevated risk of allograft rejection and drug-related adverse events [9–11].

In the maintenance phase of heart transplantation, both total conversion to a mTOR-i [12–27] or the use of combined mTOR-i and low CNI doses aimed to minimize CNI exposure [24,28–37] have been extensively tested for preservation of renal function. In the case of conversion, several randomized controlled studies [16,22,27] have confirmed the superiority of this strategy with respect to standard CNI-based immunosuppression. The recovery of renal function with this approach seems to be clearly related with early conversion [26] and with the absence of baseline proteinuria [23]. Similarly, randomized clinical trials [34–37] have demonstrated that the combined use of mTOR-i for minimizing CNI exposure portends better renal outcomes than conventional immunosuppression and, again, that the results are dependent on the time from transplantation to mTOR-i use [34,35] and the absence or presence of proteinuria at the time of mTOR-i use [37].

Up to date, there are not randomized controlled comparisons between mTOR-i based conversion and minimization strategies in the maintenance phase of heart transplantation. Two cohort studies [24,33] and one case–control study [29] have suggested slightly better renal outcomes for total conversion than for minimization strategies. Given this lack of solid information, in this study we sought to compare the real-world efficacy and safety of total conversion vs. minimization strategies in promoting renal recovery in heart transplant patients with renal dysfunction.

2. Methods

This was an investigator-driven, industry-independent, retrospective, multi-center study carried out on an intention to treat basis. The coordination between the 10 participating centers across Spain, the adjudication process, and the analysis were performed centrally according to the standards from the Spanish Registry of Heart Transplantation [38].

2.1. Patient selection

Each center analyzed all the chronic cardiac transplant recipients in whom a mTOR-i had been used between October 2001 and March 2009. For the purpose of the present study, only patients with moderate to severe renal failure (GFR < 60 mL/min/1.73 m^2) were included. Data were obtained from the Spanish Registry of Heart Transplantation and from the review of the clinical records according to a standardized form of predefined variables. The study protocol was approved by the Ethics Committee of the "Hospital Universitario Marques de Valdecilla".

2.2. Definitions

The primary end-point of the study was the rate of change in renal function from the baseline assessment (just before the introduction of a mTOR-i) to the end of follow-up. In those patients who developed end-stage renal failure requiring chronic hemodialysis during the follow-up, the estimation of renal function just before the initiation of substitutive renal therapy was used for analysis. Renal function was assessed by the estimation of GFR according to the abbreviated MDRD equation [39] at baseline and at the end of follow-up.

The initial cohort was divided according to the immunosuppressive strategy into two groups: conversion group, including patients with an intentional complete replacement of the CNI therapy with a mTOR-i (sirolimus or everolimus); minimization group, including patients with a combined use of a mTOR-i and a reduced dose of CNI.

Cardiac allograft vasculopathy was defined either angiographically (stenosis ≥50% in any major branch and/or distal pruning of secondary branches) or clinically (acute coronary syndrome or regional Q waves on ECG with correspondent wall motion abnormality by echocardiography). Allograft rejection was defined as any clinical event determined by endomyocardial biopsy, echocardiography, or clinical findings that resulted in specific anti-rejection treatment or acute augmentation of baseline immunosuppressive therapy [40]. Only infections requiring hospital admission or intravenous antibiotics were considered for analysis.

To take into account the possible influence of the time frame in which mTOR-i was introduced, the whole sample was divided into three equivalent consecutive periods of thirty months each: initial period, from November 2001 to March 2004; intermediate period, from April 2004 to October 2006; recent period, from November 2006 to March 2009. For each patient, the clinical follow-up extended until the last visit recorded between April 2009 and March 2010, or until the occurrence of death.

2.3. Statistical analysis

Continuous variables are summarized as median and 25th–75th percentiles. Categorical variables are expressed as counts and percentages. Comparisons between strategy groups were performed by the Mann–Whitney U test and by the Chi-square test, as appropriate.

In our initial cohort, many baseline characteristics were significantly different between the conversion group and the minimization group (Tables 1 and 2). To reduce the effect of strategy selection bias as a potential confounder in this observational study, we performed rigorous adjustment for the differences in the baseline characteristics by the use of propensity score matching [41]. The propensity scores were estimated without regard to outcome variables, with multiple logistic regression analysis. All covariates regarding characteristics prior to mTOR-i use were included in the full non-parsimonious model for conversion versus minimization strategies (Tables 1 and 2). The discrimination and calibration ability of the propensity score model was assessed by means of the C-statistic and the Hosmer–Lemeshow statistic. For development of the propensity score-matched pairs without replacement (a 1:1 match), the method of the nearest neighbor matching was used [42]. A propensity score difference of 0.25 was used as a maximum caliper width for matching the 2 strategy groups. After propensity score matching, the baseline covariates were compared between the 2 groups (Tables 3 and 4).

The difference between immunosuppressive strategies (conversion vs. minimization) for the change rate in GFR was analyzed by a linear fixed-effects model with repeated measures both in the entire cohort (with propensity score and duration of follow-up as covariates) and in the propensity-matched cohort. Additionally, to elucidate the factors that could distinctively influence the response of renal function according to the strategy used, we fitted a model including age at mTOR-i use (<50 years; 50–65 years; ≥65 years), sex, time from to transplantation to mTOR-i use (≤1 year; 1–5 years; >5 years), type of mTOR-i (sirolimus, everolimus), baseline GFR (<30; 30–45; 45–60 mL/min/1.73 m^2), GFR decline within the year prior to mTOR-i use (<20%; ≥20%), mTOR-i withdrawal owing to drug-related adverse events, hypertension, diabetes, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and era of mTOR-i use (initial period, intermediate period, recent period), with propensity score and duration of follow-up as covariates.

To circumvent the different baseline characteristics for conversion and minimization groups, the analysis of the clinical end points (mortality, mTOR-i withdrawal due to adverse events, infection and allograft rejection) was done in the propensity-matched cohort. Event-free survival curves were performed by the standard Kaplan–Meier methods and compared with the log-rank test. All reported p values were 2-sided, and a value of $p < 0.05$ was considered statistically significant. The statistical package SPSS 15.0 (Chicago, Il.) was used.

3. Results

The entire cohort consisted of 394 patients. A conversion strategy was used in 235 patients (59.6%) and a minimization strategy in 159 patients (40.4%). The median follow-up was 2 years, with no significant difference between groups. The main demographic, clinical and therapy-related characteristics and leading reasons for mTOR-i use of the entire population and subgroups are summarized in Tables 1 and 2. The conversion group had a significant worse baseline renal function and a higher proportion of hypertension, antecedents of non-skin malignancy and use of mycophenolate mofetil and statins than the minimization group. On the contrary, the minimization group had a higher proportion of cardiac allograft vasculopathy and use of everolimus than the conversion group. These differences were related to the different clinical indications for mTOR-i use according to the chosen strategy. The main indications were renal failure and malignancy for the conversion group, and cardiac allograft vasculopathy for the minimization group.

Propensity score matching for the entire population yielded 72 matched pairs of patients (30.6% of the conversion sample and 45.3% of the minimization sample). In the matched cohort, there were no significant between group differences for any covariates (Tables 3 and 4). Propensity matched patients had a higher baseline GFR (40.9 vs.38.2 mL/min/1.73 m^2, $p = 0.04$) and higher prevalences of diabetes (36.8% vs.23.2%, $p = 0.004$) and cardiac allograft vasculopathy (45.8% vs.23.2%, $p = 0.062$) than non matched patients.

Before mTOR-i use, the serum levels of cyclosporine were significantly lower in the conversion group than in the minimization group.