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Comparison of the effectiveness of cyclosporine and tacrolimus in preventing acute rejection and their effects on kidney functions

E. GÜNDÜZ[1], C. KEMALOĞLU[2]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Akdeniz University, Antalya, Turkey
[2]Department of Cardiovascular Surgery, Faculty of Medicine, Akdeniz University, Antalya, Turkey

Abstract. – OBJECTIVE: The aim of this study is to compare the effects of cyclosporine (CsA) and tacrolimus (TAC) on preventing acute rejection and analyze the side-effect profiles of both agents, particularly on kidney functions.

PATIENTS AND METHODS: In our study, 71 patients who underwent heart transplantation were included. For maintenance immunosuppression, 28 of these patients were treated with mycophenolate mofetil (MMF), steroid, and steroid CsA, and 43 of them were treated with MMF steroid and TAC. Endomyocardial biopsy results of the patients in the first month and the first year were compared. In the follow-ups, creatinine values and other parameters were recorded.

RESULTS: Endomyocardial biopsy (EMB) performed at 1 month showed no rejection in 12 patients (42.9%) in the CsA group, grade 1R rejection in 15 patients (53.6%), and grade 2R rejection in one patient (3.6%). In the TAC group, rejection was not detected in 25 patients (58.1%), while grade 1R rejection was diagnosed in 17 patients (39.5%) and grade 2R rejection in 1 patient (2.3%) (p=0.4). In EMBs performed in the first year, 14 patients (51.9%) in the CsA group did not have rejection, 12 patients (44.4%) had grade 1R rejection, and one patient (3.7%) had grade 2R rejection. In the TAC group, grade 0R rejection was diagnosed in 23 patients (60.5%), grade 1R rejection in 15 patients (39.5%), and grade 2R rejection was not detected. Postoperative first-week creatinine values, which were found to be higher in the CsA group, were significant compared to the TAC group (p=0.028).

CONCLUSIONS: TAC and CsA are drugs that help prevent acute rejection after heart transplantation and can be used safely in heart transplant recipients. Neither drug is superior to the other in preventing rejection. TAC may be preferred to CsA as it has fewer negative effects on kidney functions in the early postoperative period.

Key Words:
Heart transplantation, Immunosuppressive treatment, Serum creatinine levels, Early rejection.

Introduction

Heart transplantation (HT) is still the "gold standard" treatment method in patients with end-stage heart failure. One- and 5-year survival after HT is 80-85%, and 69-75% respectively[1].

Rejection is one of the most crucial complications that occurs during the early periods of HT. Rejection, seen in the first 3-6 months after transplantation and which is mostly cellular type is called acute rejection. According to a 2019 report (available at: http://www.ishlt.org) by the International Society for Heart and Lung Transplantation (IHSLT), the acute rejection-based mortality ratio between 1995 and 2018 in adult transplantation cases was stated to be 3.9% in the first 30 days, 9.8% between 31 days-1 year, 4.7% between 3-5 years and 1.9% after 5 years[2,3].

Immunosuppressive treatment in solid organ transplantations prevents early rejection and extends the life span of the patient's graft. This treatment includes induction treatment and lifelong maintenance therapy. Immunosuppressive therapy generally includes corticosteroids, calcineurin inhibitors, antiproliferative and antimetabolite agents, and poly or monoclonal antibodies. Cyclosporine (CsA), one of the calcineurin inhibitors, was the leader of this group of drugs, while tacrolimus (TAC) began to be used increasingly after the 1990s and replaced CsA in many centers. While preventing rejection, these agents may cause serious side effects such as hypertension, renal failure, diabetes mellitus (DM), hyperlipidemia, cardiac allograft vasculopathy, malignancy, and osteoporosis[4,5].

Renal functions can be impaired both in the early and late periods after HT. This is a crucial risk factor for mortality and may develop after HT due to pre- and postoperative factors, especially after the use of CsA and TAC. Acute kidney injury (AKI) after orthotopic HT is an

Corresponding Author: E. Gündüz, MD; e-mail: dregunduz@hotmail.com

important risk factor of chronic kidney disease, which may develop in the long term at a rate of approximately 14 to 18%. It has been shown in many studies[6-8] that both CsA and TAC, are nephrotoxic drugs, especially in the early period.

Endomyocardial biopsy (EMB) is the best method to diagnose rejection after HT. Biopsies are performed once a week in the first month, once a month in the first 3 months, then every 3 months until the end of the first year, and in the second and third years together with coronary angiography. Rejection attacks are diagnosed and treated early with these periodic endomyocardial biopsies[9,10].

The aim of this study is to compare the effects of CsA and TAC on preventing acute rejection and analyze the side-effect profiles of both agents, particularly on kidney functions.

Patients and Methods

In this study, the data of 103 patients who underwent HT in our clinic between 1998-2020 were evaluated retrospectively. Seventy-one patients who met al[l] the inclusion criteria were included in the study. Thirty-two patients who had primary graft failure according to endomyocardial biopsy results, death within the first year after transplantation, 1 month and 1 year patients without EMB results, patients whose kidney function values could not be reached from the database, and those using immunosuppressants other than TAC and CsA were excluded from the study (Figure 1).

The study protocol was approved by Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval number: KAEK-773). Written informed consent forms were obtained from each patient. The study was conducted in accordance with the Helsinki Declaration principles.

Of the patients, 28 received CsA, and 43 received TAC treatment. Data were collected on preoperative demographic characteristics and comorbidities (hypertension, DM, hyperlipidemia, and smoking), and etiology of heart failure (ischemic, dilated). The preoperative and postoperative first-week, first-month, and first-year renal functions were noted. A serum creatinine level above 1.3 mg/dl was accepted as renal damage. Postoperative first-month and first-year EMB results were evaluated.

For the diagnosis of rejection, EMB was performed by entering the right heart with a transjugular approach and taking at least 3-4 samples. We evaluated the diagnosis of acute cellular rejection by endomyocardial biopsy according to IHSLT criteria. We performed biopsies once a week in the first month, monthly in the first 3 months, and then every 3 months until the end of the 1st year.

Perioperative Management and Immunosuppression Regime

The biatrial technique was performed in the HTx procedure. In anesthesia induction, 500 mg (or 5-10 mg/kg) methylprednisolone is administered intravenously. The same dose of methylprednisolone was given intravenously after aortic unclamping. Methylprednisolone was administered intravenously with a dose of 125 mg at 8-hour intervals in the first 24 hours. Afterward, prednisolone was administered with a dose of 1 mg/kg orally and the dose was continued by gradually decreasing. All patients initially received a triple standard of treatment consisting of CsA or TAC, mycophenolate mofetil (MMF), and prednisolone. Everolimus was not used. CsA was administered postoperatively in two doses of 5-10 mg/kg orally and continued at 2.5-5 mg/kg. Target plasma levels of CsA during the first 3 months were 300-400 ng/mL and were decreased to 250-300 ng/mL until the 6th month, 200-250 ng/mL until 1 year, and 150-200 ng/mL at the end of the first year by monitoring the serum creatinine levels (<2 mg/dl). TAC target plasma levels were maintained at 17-23 ng/mL for up to 3 months, decreased to approximately 10 ng/mL by 6 months, to 5-8 ng/mL at 1 year, and 5 ng/mL after 1 year. MMF treatment was initiated within the first week after transplantation and was administered at a dose of 1,500-2,000 mg/day. Patients to whom the CNI was switched were not included in the retrospective analysis.

Endomyocardial Biopsy

Four or six pieces 1-2 mm in size taken with a right ventricular biopsy catheter are determined with 10% buffered formaldehyde and passed through routine tissue follow-up. Afterward, conventional Masson trichrome staining is performed to demonstrate the increase in hematoxylin-eosin and connective tissue. Rejection grading is performed in line with the intensity of lymphocyte infiltration and the presence or absence of myocyte necrosis. Acute rejection is more common in the early postoperative period; thus, biopsy controls should be performed

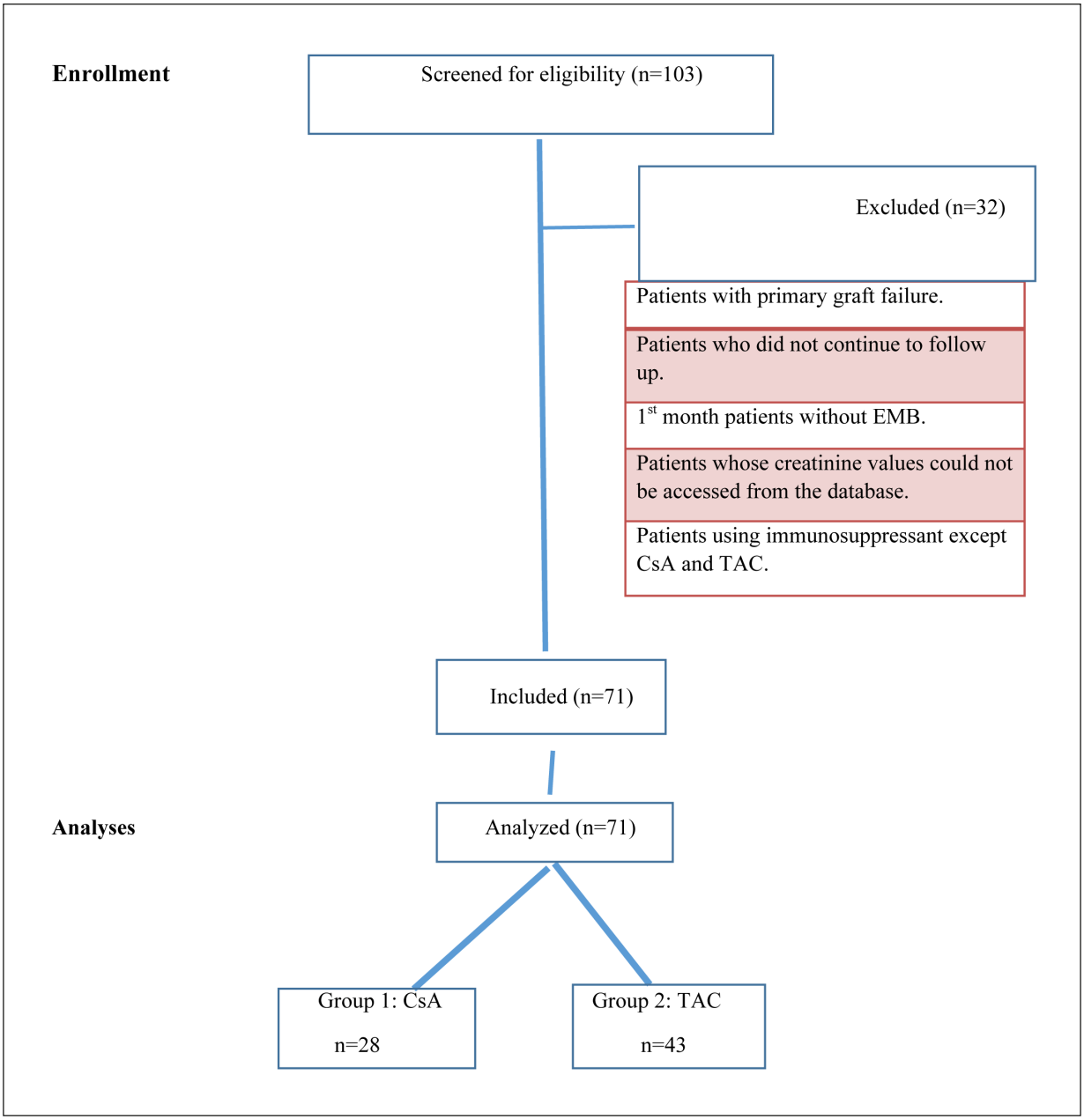

Figure 1. Flow diagram.

frequently in the first months. In the postoperative period, a biopsy is performed every week or every 10 days in the first month. Routine biopsy and controls are performed twice a month between the third month and the sixth month, and every three months after the sixth month, in patients who have not encountered any problems and are discharged. Considering the patient's rejection attacks and the clinical status, biopsy intervals are extended, starting from the second year, if possible.

Statistical Analysis

All the data included in the database have been analyzed with a Professional statistic package. Statistical analyzes were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation, median, percentage, minimum, maximum) were used to evaluate the study data. The conformity of quantitative data with the normal distribution was tested with the Shapiro-Wilk test and graphic examinations. The Student *t*-test was

used for the binary intergroup comparisons of the quantitative variables with normal distribution while Mann-Whitney U test was used for the binary inter-group comparisons of the quantitative variables without normal distribution. Wilcoxon signed-ranks test was used for the quantitative changes of 2 dependent groups. The statistical significance was set at $p<0.05$.

Results

The mean age of the patients was 46 (minimum 19, maximum 66), 15 female (21.1%), 56 male (78.9%). Twenty-eight (39.4%) of the patients received CsA, and 43 (60.6%) TAC treatment. Seven (25%) and 8 (18.6%) of the cases treated with CsA and TAC, respectively, were women. While the mean age of the patients who received CsA was 44±9.9 years, it was 44.1±12.2 in the TAC group (p=0.3). Hypertension was present in 39 (54.9%) patients. There were 18 (64.3%) hypertensive patients in the CsA group and 14 (32.6%) patients in the TAC group (p=0.009). The donors' ischemia time was 114±51.1 minutes in the CsA group and 122.9±42.7 minutes in the TAC group (p=0.105). The aortic cross-clamp time of the patients was 84±53 minutes in the CsA group and 83±48 minutes in the TAC group (p=0.932) Demographic data is given in Table I.

EMBs performed at 1 month showed no rejection in 12 patients (42.9%) in the CsA group, grade 1R rejection in 15 patients (53.6%), and grade 2R rejection in one patient (3.6%). In the TAC group, rejection was not detected in 25 patients (58.1%), while grade 1R rejection was diagnosed in 17 patients (39.5%) and grade 2R rejection in 1 patient (2.3%) (p=0.4). In EMBs performed in the first year, 14 patients (51.9%) in the CsA group did not have rejection, 12 patients (44.4%) had grade 1R rejection, and one patient (3.7%) had grade 2R rejection. In the TAC group, grade no rejection was diagnosed in 23 patients (60.5%), grade 1R rejection in 15 patients (39.5%), and grade 2R rejection was not detected. Antibody-mediated rejection was found 5 cases in both groups (p>0.5). Two patients died in the TAC group after the 1st-month biopsy was performed. One of the patients died due to primary graft failure in the postoperative 3rd month, and the other due to sepsis in the 7th month. There was no severe rejection in the first month biopsies of both patients. 3 patients in the TAC group did not come to the 1st year follow-up and EMB control (Table II).

We do not treat grade 1R rejections while we use pulse steroid treatment for grade 2R rejection (1 gr methylprednisolone for 3 days). The maintenance treatment is unchanged. Switching the CNIs may also be considered after pulse steroids. Hemodynamic stabilisation is essential. In more serious rejections, including heart muscle damage, anti-thymocyte globulin treatment is given for 10 days (daily for the first 3 days, then 4 doses every 2 days), and the maintenance treatment is stopped in this period.

Preoperative serum creatinine levels were 1.03 mg/dL (min: 0.64, max: 1.79) in the CsA group and 1.01 mg/dL (min: 0.54, max: 7.21) in the TAC

Table I. Demographic characteristics of the patients.

Characteristic	CsA n=28	TAC n=43	*p*-value
Age, years	44±9.9	41.4±12.2	0.325
Male, n (%)	21 (75)	35 (81.4)	0.519
Comorbidities, n (%)			
Hypertension	18 (64.3)	14 (32.6)	**0.009**
DM	24 (85.7)	31(88.5)	0.179
Dyslipidemia	4 (14.2)	8 (22.8)	0.635
Donor age, years	26±8	28.7±9	0.316
Aetiology, n (%)			
ICM	8 (28.6)	16 (37.2)	
DCM	18 (64)	26 (60.5)	
Others	2 (7.2)	1 (2.3)	0.510
Donor ischemic time (min)	114±51.1	122.9±42.7	0.105
Aortic cross-clamping time (min)	84±53	83±48	0.932
LVAD n (%)	2 (7.1)	1 (2.3)	0.558
IABP+ECMO, n (%)	2 (7.1)	2 (4.6)	0.644

ICM: Ischemic Cardiomyopathy, DCM: Dilated Cardiomyopathy, LVAD: Left Ventricular Assist Devices (HeartWare-Medtronic, Inc., Framingham, MA, USA), IABP: Intraortic balloon pump, ECMO: Extracorporeal membrane oxygenation.

group. There was no significant difference in preoperative serum creatinine values in patients who received CsA and TAC (p=0.933). While 10.7% of the cases with high preoperative creatinine levels were in the CsA group, 13.9% were in the TAC group. In the CsA group, serum creatinine levels in the 1st week, 1st month, and 1st year were respectively 1.08 mg/dL (min: 0.6, max: 1.8), 1.01 mg/dL (min: 0.53, max: 2.63), 1.13 mg/dL (min: 0.61, max: 3.21), and 0.77 mg/dL (min: 0.37, max: 2.6), 0.95 mg/dL (min: 0.48, max: 1.74), and 1.09 mg/dL (min: 0.55, max: 2.67) in the TAC group, respectively. The creatinine values in the first week, first month, and first year of the patients who received CsA treatment were compared. At the end of the first year, the creatinine level of the patients was found to be higher than in the pre-operative period (p=0.032). The situation was not different in patients who received TAC treatment (p=0.01). Acute renal failure did not occur in any of the cases. No significant difference was found between the patients who received CsA and TAC treatment in terms of creatinine levels in the first week, first month, and first year (Figure 2).

Left ventricular ejection fraction (LVEF) values of the cases in CsA group were 65 in the first month (min: 45, max: 70), 65 in the first year (min: 50, max: 70), and 60 (min: 59, max: 70), and 65 (min: 55, max: 70) in the TAC group, respectively. In the postoperative period, no significant difference was found in LVEF values in either the CsA or TAC groups, either among themselves or between both groups (p=0.743) (p=0.197) (Figure 3).

Table II. 1st month and 1st-year EMB results.

	CsA (n=28)	TAC (n=43)
EMB 1 month		
Grade 0R	12 (42.9%)	25 (58.1%)
Grade 1R	15 (53.6%)	17 (39.5%)
Grade 2R	1 (3.6%)	1 (2.3%)
EMB 1 year		
Grade 0R	14 (51.9%)	23 (60.5%)
Grade 1R	12 (44.4%)	15 (39.5%)
Grade 2R	1 (3.7%)	-

Discussion

In a study[11] of 157 patients comparing cyclosporine and tacrolimus for acute rejection in heart transplant patients, endomyocardial biopsy results at 6 months were evaluated. Grade 1B and higher rejection incidence was determined as 66.4% for CsA and 54% for TAC (p=0.029). The incidence of grade 3A and higher rejection was 42% for CsA and 28% for TAC (p=0.013). In our study, when the 1st-month and 1st-year EMBs were compared, no statistically significant difference was found between the CsA and TAC groups for rejection numbers. For CsA and TAC, 57.2% and

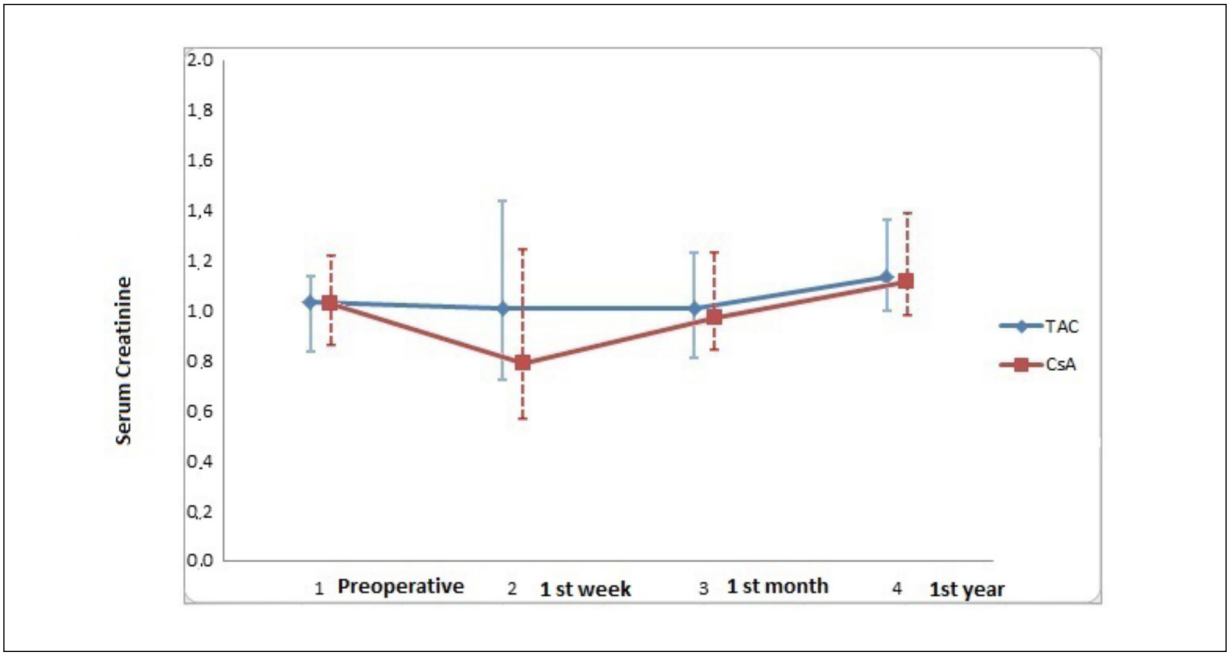

Figure 2. Serum creatinine levels of patients preoperatively and after treatment with TAC and CsA.

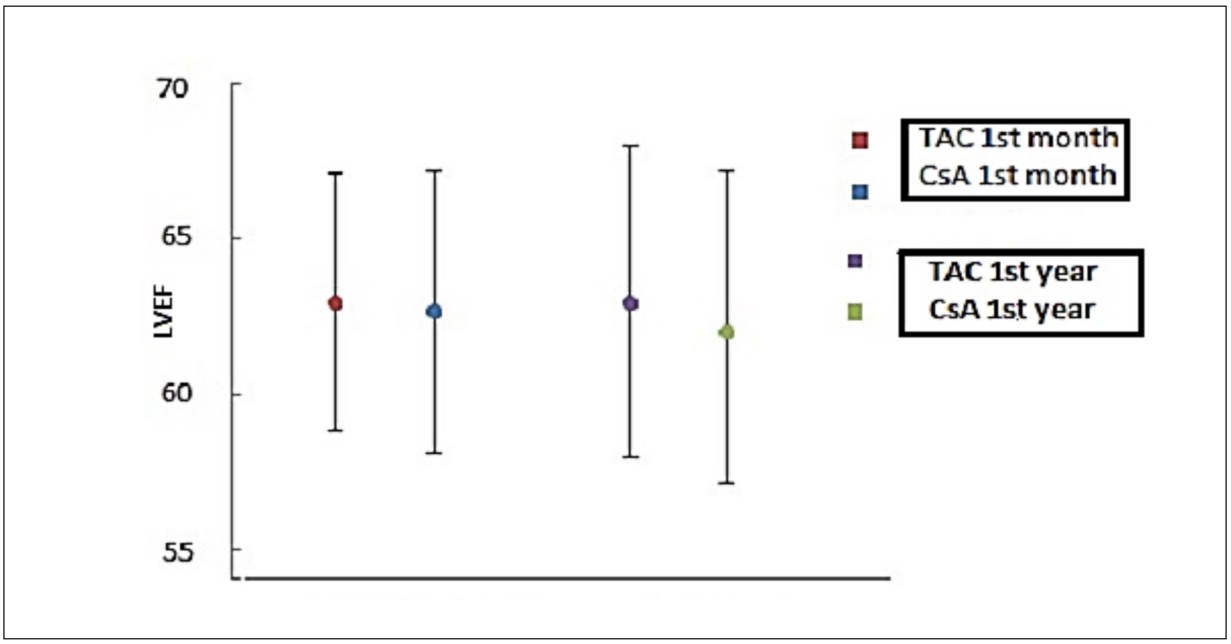

Figure 3. EF values of the patients at the end of the postoperative 1st month and 1st year.

41.8% (p=0.4) at 1 month, 48.1% and 44.4% at 1 year, respectively (p>0.5).

In another study[12] comparing CsA and TAC drugs in terms of Grade 3A or higher rejection and rejection attacks requiring treatment, in parallel with our study, no significant difference was found between the two drugs. At the same time, creatinine values in the TAC group were found to be statistically significantly lower in this study, as in our study.

In another study[1] comparing CsA and TAC in 72 patients, it was shown that both agents were not superior to each other in terms of preventing rejection and worsening renal functions.

Calcineurin inhibitors are nephrotoxic agents that can impair kidney functions while preventing early rejection in patients receiving both CsA (mainly) and TAC. Causing serious effects such as hypertension, diabetes, and hyperlipidemia, these nephrotoxic agents also contribute to chronic kidney impairment in the late period. These agents also cause acute kidney impairment (AKI), developing at a rate of 14-76% after HT[6,7]. Kidney functions may be impaired in the early period due to factors such as preoperative renal dysfunction, high creatinine, history of heart failure, donor ischemia duration, intraoperative cross-clamp duration, and fluid therapy[13,14].

AKI is defined as an increase in serum creatinine and a decrease in urine output due to decreased renal functions, and cardiac surgery-related AKI is approximately 30%[6,15]. One of the important determinants for the increase in AKI rate in the early HT postoperative period is CsA and TAC, which are calcineurin inhibitors[8]. The fact that CsA has a higher risk of nephrotoxicity than TAC is defined and known in the literature[16].

The nephrotoxic effect of calcineurin inhibitors may emerge after the first dose with vasoconstriction in afferent arterioles. These nephrotoxic effects cause an imbalance between endogenous vasoconstrictors such as endothelin and thromboxane and vasodilator factors, reducing the glomerular filtration rate (GFR), and leading to an increase in serum creatinine. This vasoconstrictor effect peaks two hours after the first oral dose. Therefore, the CsA drug level should be monitored at the end of the second hour of the first dose, for the first 24 hours, and every day[17].

In our study, preoperative, postoperative 1st-week, 1st-month, and 1st-year creatinine values were compared. 1st-week creatinine values were statistically significantly higher in CsA group patients. This height detected in the 1st week loses its statistical significance in the 1st month and 1st year. Although the increase in creatinine in the CsA group was slightly higher than in the TAC group, it was insignificant when the two groups were compared in 1st month and 1st year.

Although there was no difference between CsA and TAC group immunosuppressive drugs in preventing rejection, creatinine values were found to be significantly higher in the CSA group

in the first week. It may be beneficial to use TAC group immunosuppressive in the early period in patients at risk of cute kidney injury (AKI).

Shiraishi et al[1] did not find a difference in terms of both renal injury and acute rejection rates in 72 cases of TAC according to CsA in the first year of HT operation.

In cases where CsA is used, a correlation was found between the dose of the drug and acute renal damage. However, although we found a significant increase in creatinine (10.7%) in our cases, neither renal replacement therapy nor dialysis was required in any of the patients receiving CsA. This may be due to the fact that we used the recommended low dose.

In the literature, it was generally considered the first month and the first year as a basis for determining the early period in terms of AKI. Thongprayoon et al[17] studied 137,201 cases who had HT from 27 cohort studies. It was found that the incidence of AKI was 47%. The study reported that this severe AKI increased mortality 3.5 times in the early period (90 days) and 2.3 times in the first year.

Limitations

The small number of patients is one of the limitations of the study. Its retrospective design is another limitation. Prospective studies with a larger number of patients will contribute to the clarification of the subject.

Conclusions

TAC and CsA are drugs that help prevent acute rejection after heart transplantation and can be used safely in heart transplant patients. Neither drug is superior to the other in preventing rejection. TAC may be preferred to Csa as it has fewer negative effects on kidney functions in the early postoperative period.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee approval was obtained from the Akdeniz University Non-interventional Ethical Board (Approval number: KAEK-773).

Informed Consent

All patients provided written informed consent.

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Availability of Data and Materials

Data are available upon request to the corresponding author.

Authors' Contributions

Conception and design: Gündüz E, Kemaloğlu C; acquisition of data: Kemaloğlu C; analysis and interpretation of data: Gündüz E; drafting the article: Gündüz E; supervision: Kemaloğlu C; validation and final approval: all authors.

ORCID ID

Gündüz E: 0000-0002-0306-9770
Kemaloğlu C: 0000-0002-3326-199

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