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Safety profile of the concomitant use of atorvastatin and cyclosporine in renal transplant recipients

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Cyclosporine (CyA) and atorvastatin (AT) are often administered concomitantly to treat dyslipidemia in renal transplant recipients. However, CyA greatly increases the plasma concentration of AT; therefore, concomitant use might increase the frequency of statin-induced adverse effects. The aim of this study was to investigate whether concomitant use of CyA and AT increases intolerance of the latter agent in Japanese renal transplantation recipients. We performed a retrospective cohort analysis of renal transplant recipients aged 18 years and older who had concomitantly received AT and CyA, or tacrolimus (Tac) therapy. We defined statin intolerance as a decrease in dose or discontinuation of AT due to adverse effects. We evaluated the incidence of statin intolerance in concomitant therapy with CyA for 100 days after the initial administration of AT in comparison with Tac. A total of 144 renal transplant recipients who received AT and CyA, or Tac between January 2013 and December 2019 were included. There was no statistical difference in the incidence of statin intolerance in both the CyA (1.8%; 1/57 patients) and Tac (3.4%; 3/87 patients) groups. Concomitant use of CyA and AT might not increase the incidence of statin intolerance in Japanese renal transplant recipients.

1. Introduction

In 2018, the Japanese Society for Dialysis Therapy reported that 340.000 patients in Japan received renal dialysis (Yoshinaga et al. 2021). Kidney transplantation is the optimal renal replacement therapy because of greater longevity and better quality of life compared to dialysis therapy. To prevent rejection and improve graft survival, recipients must receive maintenance-immunosuppressive therapy, including steroids, calcineurin inhibitors (CNIs), everolimus, or mycophenolic acid. Steroids and CNIs frequently cause post-transplant dyslipidemia, which is a significant risk factor for cardiovascular disease (CVD) (Shirali and Bia 2008), the latter being the major cause of death in renal transplant patients (Stoumpos et al. 2015; Vanrenterghem et al. 2008). Therefore, strict management of lipidaemia is crucial to improve the prognosis of recipients.

Statins have a strong cholesterol-lowering action and contribute to prolonging the survival of renal transplant recipients (Wiesbauer et al. 2008). In particular, strong statins, such as atorvastatin (AT), pitavastatin, and rosuvastatin, have better low-density lipoprotein cholesterol (LDL-C)-lowering actions than standard statins. However, patients often present with statin intolerance, which is defined as "clinical or laboratory adverse experiences linked to statin treatment by validated clinical evidence and presenting with pain, impairment, or risk which justifies statin cessation or dose reduction" (Kajinami et al. 2020). The most common symptoms of statin intolerance include muscle aches, pain, weakness, and cramps, often called myalgias, and can occur in up to 15% of patients on statin therapy. As poor adherence is known to lead to a decrease in the preventative effects on atherosclerotic CVD, monitoring the incidences of statin intolerance and severity are essential to improve statin adherence (Fitchett et al. 2015).

Cyclosporine (CyA) inhibits organic anion transporting polypeptide (OATP) transporter and strongly suppresses hepatic uptake of statins *via* the OATP transporter (Maeda 2015). Therefore, concomitant use of CyA increases the area under the drug concentration curve (AUC) of statins by approximately 10-fold (Ponticelli et al. 2020), and may thus increase the risk of statin-induced adverse effects. Pitavastatin and rosuvastatin are contraindicated with CyA in Japan. Although CyA increases the AUC of AT from six to nine times, AT is the only strong statin not contraindicated with CyA in Japan. However, there are some reports of adverse effects following their concomitant use in a small number of cases. Furthermore, no reports have evaluated AT intolerance in kidney transplant recipients on CyA-based immunotherapy.

The purpose of this study was to investigate whether the concomitant use of CyA increases statin intolerance of AT in Japanese renal transplantation recipients compared to a CNI, tacrolimus (Tac), without interacting with the statin (Lemahieu et al. 2005).

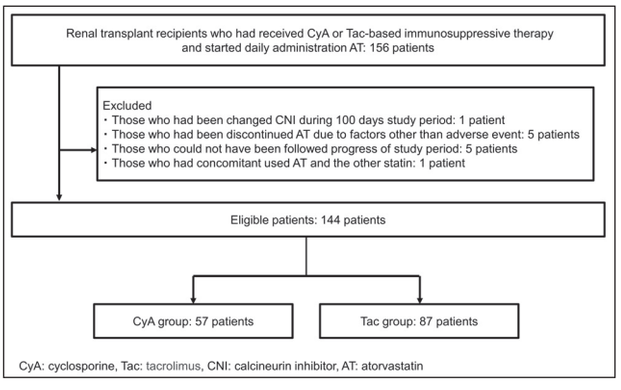

Fig.: Participant flowchart

2. Investigations and results

2.1. Patient characteristics

Figure shows a flow diagram illustrating the enrollment process of this study. A total of 156 renal transplant recipients starting on daily AT administration due to hyperlipidemia during the study period were included. Of these, 12 patients were excluded from the study because of the following reasons: 1) change in CNI (one patient); 2) AT discontinuation due to factors other than adverse events (five patients); 3) unable to follow progress during the 100 days after the initial administration of AT (five patents); 4) concomitant use of AT and other statins (one patient). Consequently, 144 patients were enrolled and divided into the CyA (57 patients) and Tac (87 patients) groups. Table 1 shows the baseline demographic and clinical characteristics of the two groups.

2.2. Safety of using AT and a CNI concomitantly within 100 days

The dose of AT was decreased or discontinued in one patient in the CyA group and in three patients in the Tac group due to symptoms suspected to be adverse events of AT administration. The patient in the CyA group experienced fatigue. Moreover, two patients in the Tac group presented with myopathy inapplicable to statin intolerance, as defined in the guide, and one patient exhibited diarrhea. There was no significant difference in the ratio of patients with statin intolerance between the CyA and Tac groups (1.8% vs. 3.4%, P=1.00). In the above-mentioned patients who presented with statin intolerance, the blood concentration of CyA was 55 ng/ml, and that of Tac was 2.8, 4.9, and 10.0 ng/ml.

Table 1: Baseline demographic and clinical characteristics

		CyA group (n=57)	Tac group (n=87)	p-value
Baseline clinical characteristics				
age	Median (min-max)	50 (21-77)	53 (25-75)	0.136[a]
sex	male	35	55	0.861[b]
	female	22	32	
preemptive transplantation	Yes	6	9	0.741[b]
	No	47	68	
	unknown	4	10	
blood type of donor and recipient	compatible	24	42	0.778[b]
	incompatible	32	43	
	unknown	1	2	
rejection	Yes	14	20	0.977[b]
	Borderline	1	1	
	No	39	62	
	Unknown	3	4	
history of taking other statin after transplantation	Yes	6	7	0.767[b]
	No	51	80	
Laboratory data just before AT treatment				
CK (U/L)	Median (min-max)	68 (16-183)	62 (17-1517)	0.746[a]
T-bil (mg/dl)	Median (min-max)	0.5 (0.3-2.2)	0.6 (0.2-2.3)	0.623[a]
AST (U/L)	Median (min-max)	17 (7-37)	17 (8-44)	0.46[a]
ALT (U/L)	Median (min-max)	14 (4-33)	14 (5-58)	0.542[a]
eGFR (mL/min/1.73 m^2)	Median (min-max)	40.88 (6.25-66.48)	42.28 (6.67-81.42)	0.314[a]
Start dose of AT				
5 mg		22 (38.6%)	38 (43.7%)	
10 mg		34 (59.6%)	45 (51.7%)	0.526[b]
20 mg		1 (1.7%)	4 (4.6%)	
CNI blood concentration at the start of AT (µg/ml)				
Median (min-max)		77 (30-316)	5.1 (1.8-18)	-

[a]Mann-Whitney U tests, [b]Fisher's exact test
CyA: cyclosporine, Tac: tacrolimus, CNI: calcineurin inhibitor, AT: atorvastatin
CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase
T-bil: total bilirubin, eGFR: estimated glomerular filtration rate

Table 2: Adverse events of AT during 100 days

(a) Frequency of adverse events based on the 2018 statin intolerance clinical guide

	CyA group (n=57)	Tac group (n=87)
hepatopathy	0 (0%)	0 (0%)
myopathy	0 (0%)	0 (0%)

(b) Frequency of statin intolerance and adverse events that caused AT dose reduction or discontinuation

		CyA group (n=57)	Tac group (n=87)	p-value
Statin intolerance		1 (1.8%)	3 (3.4%)	1.00[a]
	fatigue	1 (1.8%)	0 (0%)	
	diarrhea	0 (0%)	1 (1.1%)	
	myopathy	0 (0%)	2 (2.3%)	

[a]Fisher's exact test
CyA: cyclosporine, Tac: tacrolimus, AT: atorvastatin

3. Discussion

The present retrospective study evaluated whether the concomitant use of CyA increased the incidence of statin intolerance induced by AT in renal transplant patients. Our findings showed that the concomitant use of CyA did not increase statin intolerance of AT in renal transplant recipients compared to Tac.

Herein, the incidences of statin intolerance due to AT were 1.8% and 3.4 % in patients taking CyA and Tac, respectively. Although no reports on statin intolerance in kidney transplant patients have been published, some studies reported that the frequency of statin intolerance varies from 0% to 10% in Japanese non-kidney transplant patients with dyslipidemia (Kajinami et al. 2020). Renal dysfunction has been identified as a risk factor for the adverse effects of statins (Kajinami et al. 2020). Therefore, the incidence of statin intolerance in kidney transplant patients might be higher than that in non-renal transplant recipients. Contrary to our expectations, the observed incidence was lower than expected. This may help explain the low incidence of using AT in patients with renal dysfunction and its relatively tolerability among statins (Kajinami et al. 2020). Additionally, CNIs or steroids are effective in statin-induced myopathy in which the anti-3-hydroxy-3-methylglutaryl-CoA reductase antibody is involved (Watanabe et al. 2016; Tiniakou 2020). Therefore, immunosuppressive therapy may suppress statin-induced myopathy. Moreover, renal transplant recipients are frequently followed up with blood sampling, thus the nocebo effect, which has become a problem in recent years, can be distinguished (Herrett et al. 2021). This study demonstrates that renal transplant recipients on CyA did not have an increased risk of statin intolerance.

A previous report showed that serum levels of AT were elevated in CyA-treated renal transplant recipients (Hermann et al. 2004). Although it is conceivable that the incidence of statin intolerance of AT in renal transplant recipients who received CyA might be higher than that in those who received Tac, our results do not support this notion. Racial differences between Japanese and Western patients may explain why concomitant use of CyA did not increase statin-related intolerance. A meta-analysis reported that patients of Western origin need a three to four-fold greater dosage of AT than Asians to achieve similar LDL-C reduction (Naito et al. 2017). This dose difference could be explained by genetic differences in single nucleotide polymorphisms of the solute carrier organic anion transporter family member 1B1 gene and the drug efflux transporter ATP-binding cassette G2 expression gene (Fitchett et al. 2015; Naito et al. 2017). The recommended dose of AT is less than 20 mg/day in Japan and 80 mg/day in the United States. Furthermore, a pooled analysis of short time trials reported that among Asian patients who received AT 40 mg/day, 80 mg/day, and placebo, the proportion of those who discontinued statin therapy due to treatment-related adverse effects was 1.7, 4.6, and 2.6%, respectively (Chan et al. 2016). Owing to this, an AT dose much higher than 20 mg/day would be tolerable for Asian patients; however, most patients received a dose lower than 10 mg/day in this study, thus blood levels of AT during concomitant use with CyA might have been lower than those that would cause side effects. Therefore, it is conceivable that statin intolerance from AT use does not increase even if CyA is concomitantly used.

This study has several limitations. First, there may be some confounders due to its retrospective nature. Additionally, our sample size was not large enough to confirm rare adverse effects, such as statin-induced rhabdomyolysis whose incidence is reported to be 0.001%. Therefore, a larger clinical study or big data analysis is warranted to confirm the exact effects of concomitant CyA use on statin intolerance. Second, we could not examine the effect of high-concentration CyA on statin intolerance because most patients in this study started AT 3 months after transplant. In fact, the CyA concentration in one patient who discontinued AT during the study period owing to adverse effects was 77 ng/ml. In general, CyA concentration should be kept in the range of 150–200 ng/ml within 1 month and under 100 ng/ml after 3 months (Hirukawa et al. 2017). Therefore, examining statin intolerance in patients with high concentrations of CyA is also important. Finally, we could not examine the effects of genetic factors due to the retrospective nature of the study.

In conclusion, concomitant use of CyA might not increase the incidence of statin intolerance of AT in Japanese renal transplant recipients compared with Tac. Additionally, the rate of statin intolerance of AT was 1.8%, which is equal to or lower than that in non-renal transplantation recipients. This result may support the current treatment plan to improve dyslipidemia in renal transplant patients undergoing maintenance-immunosuppressive therapy.

4. Experimental

4.1. Study design and participants

We conducted a retrospective cohort analysis of renal transplant recipients aged ≥ 18 years who had received concomitant therapy of AT and CNIs between January 2013 and December 2019 at the urology department of Osaka City University Hospital (Osaka, Japan). The observation period was defined as 100 days from the initial administration of AT. We excluded patients who had switched between CNIs and discontinued AT or switched between statins owing to factors other than adverse events during the study period. Additional exclusion criteria included the concomitant use of AT and other statins and loss to follow-up during the study period. This study was approved by the Human Subjects Review Committee of Osaka City University and performed in accordance with the ethical principles for medical research outlined in the Declaration of Helsinki 1964 and per subsequent revisions (https://www.wma.net/).

4.2. Data collection

The following data were collected from the patients' medical records: age, sex, preemptive transplantation, blood type compatibility of donor and recipient, rejection after transplantation, history of other statins (before or after transplantation), start dose of AT, blood concentration of CNIs at the start of AT administration, laboratory values, and adverse effects caused by AT. Laboratory values included creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-bil), and the estimated glomerular filtration rate (eGFR).

4.3. Assessment of statin intolerance

In this study, hepatopathy and myopathy were assessed according to the "statin intolerance clinical guide, 2018" (Kajinami et al. 2020). Hepatopathy was defined as

ALT ≥ 3×upper limit of normal (ULN) or T-bil ≥ 2×ULN. Myopathy was defined as serum CK ≥ 4×ULN or presence of statin-associated muscle symptoms (SAMS). We followed the progress of the patients during the 100 days after the initial administration of AT and defined statin intolerance as a decrease or discontinuation of AT due to adverse effects during the study period.

4.4. Statistical analysis

Categorical data were analyzed using Fisher's exact test, while Mann–Whitney U tests were used for comparisons between continuous variables. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using Easy R, version 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

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Conflict of interests: All other authors declare that they have no conflicts of interest.

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