Effect of Immunosuppressive Treatment on Carotid Atherosclerosis in Renal Transplant Recipients

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ABSTRACT

Background. The aim of this study was to compare the effect of immunosuppressive regimens using either mammalian target of rapamycin inhibitors (mTORi) or calcineurin inhibitors (CNI) on the risk of atherosclerosis in renal transplant patients.

Materials and Methods. The study involved a group of 24 recipients treated with mTORi (mTORi group) and a group of 20 recipients treated with immunosuppressive regimen based on CNI (CNI group). Laboratory and clinical markers of cardiovascular risk in both groups were investigated. Carotid atherosclerosis was evaluated by measurement of the intima media thickness (IMT) of the common and internal carotid artery walls and detection of carotid plaques by a high-resolution ultrasonography. The study was performed 3–24 years after transplantation.

Results. The mTORi group showed higher level of total cholesterol (242 vs 201 mg/dL; $P < .004$), low-density lipoprotein cholesterol (140 vs 116 mg/dL; $P < .05$), and triglycerides (226 vs 168 mg/dL; $P < .01$). Posttransplant diabetes developed in 34% of mTORi group compared with 25% in the CNI group. The mean of IMT (left and right) of common and internal carotid arteries was similar in both groups. Carotid plaques were detected in 46% of patients from the mTORi group and 25% from CNI group ($P < .02$). The presence of carotid plaques combined with an IMT of >0.9 mm were associated with male gender, mTORi treatment ($P = .03$), and cardiovascular events. The incidence of coronary heart disease was higher in mTORi group than in CNI group (53% vs 20%; $P = .03$).

Conclusions. There was not beneficial effect of immunosuppressive treatment with mTORi on carotid atherosclerosis in renal transplant patients.

CARDIOVASCULAR DISEASE is a major cause of morbidity and mortality in kidney transplant recipients. It is caused by preexisting cardiovascular disease, which is additionally exacerbated by side effects of immunosuppressive treatment. The choice of cardioprotective immunosuppression could improve the long-term allograft and patient survival. Calcineurin inhibitors (CNI), the main component of immunosuppression, increase the level of endothelin (which induces vasoconstriction), activate sympathetic nervous system, abrogate nitric oxide-induced vasodilatation, cause sodium retention (leading to hypertension), nephrotoxicity, and metabolic disorders.

There are inconsistent data on the influence of mammalian target of rapamycin inhibitors (mTORi) on cardiovascular system and the risk of death. This group of drugs may cause dose-dependent hyperlipidemia [1], endothelial dysfunction, diabetes [2], and proteinuria as a consequence of podocyte injury [3]. Numerous evidence from animal and clinical studies (mainly from heart transplantation and stent delivery of mTORi) indicate that mTORi have antiatherosclerotic and protective effect on coronary artery disease. The pleiotropic antiatherosclerotic effect of mTOR depends on the inhibition of endothelial and vascular smooth cell proliferation [4],

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macrophage and lipid accumulation in the atherosclerotic plaque, and impairment of lipid synthesis. These mechanisms may control plaque growth and destabilization.

The impact of mTORi on atherosclerosis development in kidney transplant patients may be evaluated by ultrasound measurement of carotid intima media thickness (IMT). IMT is used as a measure of vascular remodeling and asymptomatic atherosclerosis. Increased carotid IMT is associated with elevated risk of cardiovascular events.

The aim of this study was to compare the effect of immunosuppressive regimens using either mTORi or CNI on the carotid atherosclerosis in renal transplant patients.

MATERIALS AND METHODS

A total of 44 patients after kidney transplantation transplanted between 1987 and 2013 was included in the study. Of these patients, 24 were treated with a sirolimus or everolimus regimen (mTORi group). Seven patients received additionally prednisone, 13 mycophenolate mofetil and prednisone; 2 patients received reduced dose of cyclosporine and 2 reduced dose of tacrolimus and prednisone. Six patients received mTORi de novo after transplantation; the remaining patients were converted from cyclosporine or tacrolimus to mTORi 60 ± 59 months after transplantation. The cause of conversion was nephrotoxicity of CNI and malignancy (mainly skin). Average time of observation for cardiovascular complications of the patients from mTORi group was 57 ± 37 months.

A second group of 20 patients were treated with CNI, including 16 patients treated with tacrolimus, mycophenolate mofetil, and prednisone, and 4 patients treated with cyclosporine A, mycophenolate mofetil and prednisone (CNI group). In this group, the immunosuppressive regimen was unchanged from the time of transplantation. Average time of observation for cardiovascular complications of the patients from CNI group was 105 ± 58 months.

Patients with diabetes before transplantation were excluded from the study.

Clinical data gathered included age, time on dialysis before transplantation, time after transplantation at the moment of ultrasound evaluations, body mass index, and the number of antihypertensive drugs were evaluated. Analysis included also laboratory data: creatinine, cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, glycated hemoglobin, and proteinuria. The patients were observed for cardiovascular complications during the whole period of treatment with mTORi or CNI.

Carotid atherosclerosis was evaluated by measurement of the IMT of the common and internal carotid artery walls and detection of carotid plaques on high-resolution ultrasonography (Fig 1). IMT was measured according to the accepted methodology [5], using ultrasound Vivid 7 Dimension (GE, Port Washington, NY) device equipped with a 12-MHz linear array transducer and an automatic protocol of IMT measurement applying the grayscale analysis. Initially, the posterior wall of the left common carotid artery approximately 1 cm before the bifurcation was visualized in the longitudinal view (Fig 2). Then, after picture freezing a fragment of the artery comprising ≥200 points was marked. Using computer software, the mean value, maximum, and standard deviation of IMT were calculated. Subsequently, the procedure was repeated with for the right common carotid artery. The arithmetic averages of mean and maximum values on both sides were included into statistical analysis. The thickening of the carotid wall of ≥14 mm on the length vessel of >10 mm was considered as an atherosclerotic plaque. When a plaque was present in the place of measurement of IMT, the IMT estimation was not carried. The study was performed 3–24 years (103 ± 56 months mTORi group, 105 ± 62 in CNI group) after transplantation. All the patients gave informed consent to take part in this study.

Data were analyzed by comparison of the mean values of 2 series using the Student *t*-test.

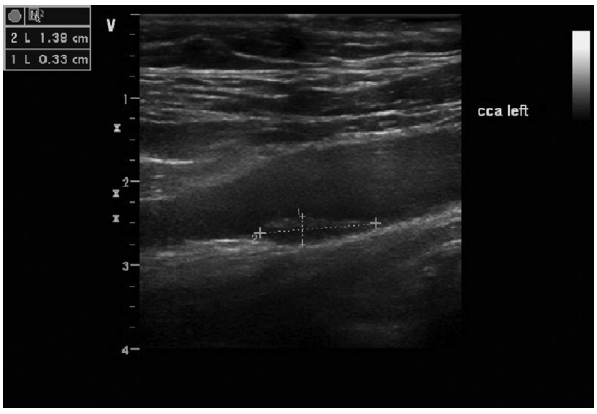

Fig 1. A typical appearance of atherosclerotic lesion. Hypoechoic plaque at the bifurcation of the common carotid artery. Atherosclerotic plaque observed in one of the patients treated with mammalian target of rapamycin inhibitors.

RESULTS

Demographic and clinical data in the examined groups of patients treated with mTORi or CNI are presented in Table 1. The patients from mTORi group were dialyzed for 34 ± 28.4 months before transplantation and patients from CNI group for 29 ± 17.4 months ($P = .5$). Laboratory data before transplantation did not differ significantly between the groups: serum level of creatinine was 6.98 ± 2.4 mg/dL

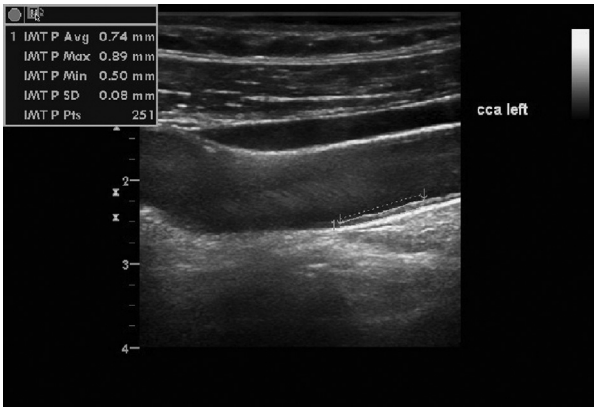

Fig 2. Automatic measurement of intima media thickness (IMT) of the posterior wall of the common carotid artery. Abbreviations: Avg, average; Max, maximal; Min, minimal; SD, standard deviation. In this patient measurement, included 251 points. cca, common carotid artery.