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Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Early Period after Kidney Transplantation

Lidija Orlić, Ivana Mikolašević, Branka Sladoje-Martinović, Ivan Bubić, Martina Pavletić-Peršić and Sanjin Rački

University of Rijeka, University Hospital Rijeka, Department of Nephrology and Dialysis, Rijeka, Croatia

A B S T R A C T

The role of renin-angiotensin system inhibitors (ACE-inhibitors) or angiotensin receptor blockers (ARB) in the renal transplant recipients (RTRs) is incompletely defined and according to the current guidelines they should be initiated after six months post-transplantation. The aim of the present paper is to evaluate the efficiency and safety of early (within six months post-transplantation) versus late (after six months post-transplantation) initiation of ACE-inhibitors or ARB in RTRs. The study group compromised of 108 RTRs (50 male and 58 female) who received a kidney transplant. Beside other prescribed antihypertensive drugs all of them took and ACE inhibitors or ARB in order to achieve blood pressure control. For this analysis purpose, recipients were stratified into two groups according to the time of ACE inhibitors/ARB initiation into early (within six months post-transplantation) and late (after six months after transplantation) group. For each patient haemoglobin, serum creatinine and potassium levels were analyzed at the beginning of ACE inhibitors/ARB introduction and at the end of the first, third, sixth and twelfth month. In the 54 (50%) of the 108 patients ACE inhibitors/ARB were initiated within six months post-transplantation and in 49 (90.7%) of them within three months (in 29 patients within one month; in 13 within two months; in 7 within 3 months) post-transplantation. In additional 54 (50%) patients ACE inhibitors/ARB were initiated, but after six months post-transplantation. There was no statistically significant difference between the two groups related to age or gender and due to the duration of dialysis treatment before the transplantation. Analyzing the haemoglobin, creatinine and potassium serum levels after initiation of therapy with ACE inhibitors/ARB trough observed period we did not found any statistically significant difference in all measured parameters between the two groups of patients and also within the same group of patients. Therefore, according to experience from our Institution early initiation of ACE inhibitors or ARB appears to be safe in carefully selected recipients with relatively good early graft function.

Key words: *renin-angiotensin system, angiotensin receptor blockers, renal transplant recipients, arterial hypertension, prescribe*

Introduction

Despite all improvements in patients and graft survival, renal transplant recipients (RTRs) continue to dye prematurely due to accelerated cardiovascular disease (CVD)[1]. Arterial hypertension (AH) is one of the important factors that have an impact on cardiovascular morbidity and mortality in general population and also in transplant patients. The prevalence of AH is about 60% to 90% in RTRs[2,3]. With traditional risk factors of AH in RTRs additional role has impact of an immunosuppressive therapy. It has been show that calcineurin inhibitors (CNIs) and glucocorticoids (GCs) can exert hypertensive effect while azathioprine, mycophenolate mofetil (MMF) and mTOR inhibitors do not interfere with blood pressure. The other factors of post-transplant hypertension are: allograft dysfunction, transplant renal artery stenosis, age of donor and the presence of native kidneys[2,4].

The majority of RTRs develop AH within one year post-transplantation[2]. The current importance of elevated blood pressure is lying in the fact that it can result in decreased allograft survival that was shown by many

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authors as well as by Collaborative Transplant Study[5]. Also AH is associated with left ventricular hypertrophy, with the latter being an independent risk factor for heart failure and death in RTRs. The current recommendations include RTRs as a special population with a recommended blood pressure of less that 130/80 mmHg[6–8], but poorly controlled blood pressure is common among RTRs and according to the literature only 17–35% of RTRs achieve the target blood pressure (<130/80 mmHg)[2,9,10]. All first- and second-line antihypertensive drugs can be used for RTRs to control blood pressure[6,7,8]. In most transplant centres calcium-channel blockers (CCB) are the most common prescribed drugs in the immediate postrenal transplant phase because, in addition to proven antihypertensive efficacy, it minimizes calcineurin inhibitors (CNIs)-induced systemic and renal vasoconstriction[2,4]. Furthermore, beta blockers (BB) are widely recommended and are first-line treatment in the RTRs with coronary heart disease, hart failure and arrhythmias[2,11]. On the other hand, the role of renin-angiotensin system inhibitors (ACE-inhibitors) or angiotensin receptor blockers (ARB) in the RTRs is incompletely defined and according to the current guidelines they should be initiated after six months post-transplantation[6–8]. Therefore, many clinicians add these drugs to the regimen later on, when the kidney transplant is functioning well and the serum creatinine has stabilized. This is mainly due to the fact that they may cause hyperkalemia and may induce anaemia, as well as in combination with a CNI-induced vascular disease they can induce a moderate decline in glomerular filtration[2,12,13]. But, because of their numerous well documented »positive« effects, these drugs are the most common prescribed antihypertensives in the general population in our country[14,15].

Only 20% of RTRs take one antihypertensive drug, while in the majority of RTRs the pharmacological treatment of AH is based on combination of two or more antihypertensives in order to achieve target blood pressure. In order to achieve blood pressure control some clinicians prescribe ACE inhibitors or ARB much earlier than is currently recommended[3,16].

According to these observations, the aim of the present paper is to evaluate the efficiency and safety of early (within six months post-transplantation) versus late (after six months post-transplantation) initiation of ACE--inhibitors or ARB in RTRs.

Patients and Methods

Patients

The study group compromised of 108 RTRs (50 male and 58 female) who received a kidney transplant at our hospital between 2001 to 2011th. Beside the other prescribed antihypertensive drugs all of the patients (from the both groups) took and ACE inhibitors or ARB due to bad blood pressure control. The decision was made by nephrologists. Six patients received a kidney from a living related donor and 102 patients received a cadaveric kidney transplant. The average age was 54.1±12.4 (range from 23 to 72) years. Dialysis treatment before transplantation lasted on average 50±50.9 (range from 1 to 254) months. At the end of the observed period, 63 (58.3%) patients had creatinine lower than 120 μmol/L, while 45 (41.7%) had a level higher than 120 μmol/L,

For this analysis purpose, recipients were stratified into two groups according to the time of ACE inhibitors/ ARB initiation into early (within six months post-transplantation) and late (after six months after transplantation) group. All patients received triple immunosuppressive therapy including a CNI/MMF/GCs and induction with IL-2 receptor blockers (daclizumab or basiliximab). As a maintenance therapy the most of them received CNIs (tacrolimus or cyclosporine) and MMF, with or without low dose of GCs. Furthermore, as late maintenance therapy a mTOR inhibitors were introduced in 6 patients due to CNI-nephrotoxicity or a history of tumours occurrence. Patient's characteristics are shown Table 1.

Method

This is retrospective observation study. For the present study, we used the usual medical records in patients with RTRs. For each patient haemoglobin, serum creatinine and potassium levels were analyzed at the beginning of ACE inhibitors/ARB introduction and at the end of the first, third, sixth and twelfth month by standard clinical chemistry techniques. Immunosuppressive and antihypertensive therapy was performed by nephrologists.

Blood pressure was measured with a standard mercury sphygmomanometer during regular out-patient examinations. We took as the criterion for defining arterial hypertension a systolic blood pressure (SP) ≥140 mmHg and a diastolic pressure (DP) ≥90 mmHg or the routine use of antihypertension therapy and as a target blood pressure we took a SP<130 and DP<80 mmHg.

Statistical analysis

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by chi-square test. Testing the importance of the difference of two independent groups were performed using t-test and ANOVA. P-value <0.05 was considered to be statistically significant. Statistical analysis was made using MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium).

Results

In the 54 (50%) of the 108 analyzed patients ACE inhibitors/ARB were initiated within six months post--transplantation, and in 49 (90.7%) of them within three months (in 29 patients within one month; in 13 within two months; in 7 within 3 months) post-transplantation. Of them 25 (46.3%) patients were taken ACE inhibitors, while 29 (53.7%) patients were taken ARB (p=NS). The

TABLE 1
DEMOGRAPHIC CHARACTERISTICS IN THE STUDY PATIENTS

	ACE/ARB within 6 months	ACE/ARB after 6 months	p
Total, N (%)	54 (50%)	54 (50%)	NS
Male, N (%)	24 (44.4%)	26 (48.1%)	NS
Female, N (%)	30 (55.6%)	28 (51.9%)	NS
Duration of RRT prior to tx (months)	49.6±45.1	48.4±49.4	NS
Age at transplant (y)	50.4±12.5	46.6±13.5	NS
Time since ACE/ARB initiation (months)	1.8±1.2	30.4±32.6	
N(%)			
Etiology:			
Glomerulonephritis	20 (37%)	22 (40.7%)	NS
Pyelonephritis	6 (11.1%)	8 (14.8%)	NS
Nondiabetic nephrop	9 (16.7%)	7 (13%)	NS
Diabetic nephropathy	4 (7.4%)	4 (7.4%)	NS
Polycystic kidney disease	5 (9.3%)	4 (7.4%)	NS
Other	10 (18.5%)	9 (16.7%)	NS
Corticosteroid use	47 (87%)	50 (90.7%)	NS
CNIs use			
Tacrolimus	38 (70.4%)	24 (44.4%)	0.011
Sandimmun	9 (16.7%)	22 (40.7%)	0.011
MMF	49 (90.7%)	49 (90.7%)	NS
m-TOR	5 (9.3%)	3 (5.6%)	NS
Concomitant aspirin use	27 (50%)	27 (50%)	NS
Concomitant statin use	27 (50%)	28 (51.9%)	NS
BB use	35 (64.8%)	30 (55.6%)	NS
CCB use	42 (77.8%)	40 (74.1%)	NS
CCB and BB use	25 (46.3%)	24 (44.4%)	NS
Diuretic use	18 (33.3%)	20 (37%)	NS

ACE – ACE inhibitors, ARB – angiotensin receptor blockers, m – months, y – years, nondiabetic nephrop – non-diabetic nephropathy of vascular origin, BB – beta blockers, CCB – calcium channel blockers CNIs – calcineurin inhibitors, GCs – glucocorticoids, MMF – mycophenolate mofetil, NS – non-significant, RAAS – renin-angiotensin-aldosteron inhibitors, RRT – renal replacement therapy, tx – transplantation

most common used ACE inhibitor was lisinopril (16 patients), while the most common used ARB was telmisartan (19 patients). One (1.9%) patient was treated with one antihypertensive drug, 17 (31.5%) with two, 20 (37%) with three and 16 (29.6%) patients with more than three antihypertensive drugs.

In additional 54 (50%) patients ACE inhibitors/ARB were initiated, but after six months post-transplantation. Of them 27 (50%) patients were taken ACE inhibitors, while 27 (50%) patients were taken ARB (p=NS). The most common used ACE inhibitor was ramipril (11 patients) and most common used ARB was telmisartan (17 patients). In this group, five (9.3%) patients were treated with one antihypertensive drug, 21 (38.9%) with two, 18 (33.3%) with three and 10 (18.5%) patients with more than three antihypertensive drugs.

None of the analyzed patients were treated with combination of ACE inhibitors and ARB.

Demographic and clinical characteristics of the analyzed 108 patients stratified by the time of ACE inhibitors/ARB initiation status are shown in Table 1. There was no statistically significant difference between the two groups related to age or gender and due to the duration of dialysis treatment before the transplantation. On the other hand, patients from the group two had statistically more frequently prescribed a cyclosporine as a part of their maintenance immunosuppressive therapy.

Analyzing the haemoglobin, creatinine and potassium serum levels after initiation of therapy with ACE inhibitors/ARB trough observed period we did not find any statistically significant difference in all measured parameters between the two groups of patients and also within the same group of patients (Table 2a, 2b and 2c). Although we did not find statistically significant difference, we have noticed that at the end of the observed period 33 (61.1%) patients from the first group (ACE inhibitors/ARB <6 months) had creatinine <120 μmol/L, while only 26 (48.1%) patients from the second group had creatinine <120 μmol/L.

None of the patients hadn't side effect such as angioedema. In the first group, four patients had potassium values above the reference value (>5.1 mmol/L) after the follow-up of one month, two patients after three months, four after six months and one patient after the follow up of 12 months. Furthermore, analyzing the occurence of hyperkalemia in the second group of patients we have found that two patients had potassium values above the reference value after the follow-up of one month, one patient after three months, three after six months and two patients after the follow up of 12 months. None of the patients from the both groups and out the whole observed period hadn't potassium value of more than 5.6 mmol/L and didn't require treatment.

After the follow-up of 12 months we have noticed that only 14 (25.9%) patients in the first group and 13 (24.1%) patients in the second group achieved the target blood pressure (<130/80 mmHg) (p=NS).

Discussion

Hypertension is a common concomitant disease in RTRs, and in most cases requiring initiation of antihypertensive therapy to achieve target blood pressure. Specific recommendations for this particular population are lacking and data about using different classes of antihypertensive are incompletely defined. Although, the current guidelines recommended that RTRs should be treated with any class of antihypertensive agents. Especially when urine protein excretion is significant (>1 g/d)

TABLE 2a
COMPARASION OF HAEMOGLOBIN VALUES IN THE TWO GROUPS OF PATIENTS DURING THE OBSERVED PERIOD

Time since ACE /ARB initiation	ACE/ARB within 6 months post-tx	ACE /ARB after 6 months post-tx	p
Haemoglobin (g/L)			
0. month	125.3±13.1	130±16.9	NS
1. month	125.3±13.1	128.9±17.4	NS
3. month	132.3±17.9	132±18.2	NS
6. month	132.2±9.5	129.5±16.3	NS
12. month	132.1±11.8	132±17.7	NS
p (ANOVA)	NS	NS	

ACE – ACE inhibitors, ARB – angiotensin receptor blockers, tx – transplantation, NS – non-significant

TABLE 2b
COMPARASION OF CREATININE VALUES IN THE TWO GROUPS OF PATIENTS IN THE OBSERVED PERIOD

Time since ACE /ARB initiation	ACE /ARB within 6 months post-tx	ACE /ARB after 6 months post-tx	p
Creatinine (μmol/L)			
0. month	125.2±57.3	127.2±48.7	NS
1. month	125.4±57.3	127.2±49.7	NS
3. month	112.7±31	121.6±37.3	NS
6. month	111.6±28.7	123.2±38.8	NS
12. month	109.8±29.5	120.9±36.6	NS
p (ANOVA)	NS	NS	

ACE – ACE inhibitors, ARB – angiotensin receptor blockers, tx – transplantation, NS – non-significant

TABLE 2c
COMPARASION OF POTASSIUM VALUES IN THE TWO GROUPS OF PATIENTS IN THE OBSERVED PERIOD

Time since ACE /ARB initiation	ACE /ARB within 6 months post-tx	ACE /ARB after 6 months post-tx	p
Potassium (mmol/L)			
0. month	4.3±0.5	4.3±0.4	NS
1. month	4.6±0.5	4.4±0.5	NS
3. month	4.8±0.4	4.3±0.5	NS
6. month	5.1±5.4	4.4±0.9	NS
12. month	4.4±0.4	4.4±0.6	NS
p (ANOVA)	NS	NS	

ACE – ACE inhibitors, ARB – angiotensin receptor blockers, tx – transplantation, NS – non-significant

ACE inhibitors or ARB are recommended as a first line treatment. The main goal of treatment is to achieve blood pressure control and possibly achieve the target value[6–8].

CCBs are an attractive option in any period following transplantation and for early treatment of hypertension after transplantation[2,17,18]. Their clinical usefulness was documented by recent meta-analysis that has showed that CCBs reduce the risk of graft loss by approximately 25% and improve graft function[19]. On the other hand, other drugs, such as ACE inhibitors or ARB are not universally recommended, especially within first six months post-transplantation. This is mainly due to several reasons. For the first, the combination of ACE-inhibitors or ARB and CNI-induced vascular disease can induce a moderate decline in glomerular filtration rate. Secondly, CNIs tends to raise the plasma potassium levels and this phenomenon can be exacerbated by an ACE-inhibitors or ARB. And thirdly they can induce anaemia in RTRs, lowering the haemoglobin levels by as much as 5–10% via a mechanism that may be enhanced by CNIs[2,6–8,18]. In the present study in a great proportion of patients ACE inhibitors or ARB were initiated within first six months post-transplantation, mainly within first three months, in patients with an initial graft function stabilisation. Our observations shows that early initiation of ACE inhibitors or ARB did not have negative impact on graft function, serum potassium and haemoglobin levels compared with those recipients with late ACE inhibitors or ARB initiation. Rather, after the one year of follow-up a more recipients with early ACE inhibitors or ARB initiation had creatinine <120 μmol/L, Although there was no statistically significant difference in serum creatinine values between the two groups of patients as well as within the same group during the whole observed period, a tendency of a lower creatinine values were noticed in the patients with the early ACE inhibitors/ARB initiation and thus maybe the explanation for our results at the end of the observed period. Pointing a potential safe early initiation of ACE inhibitors or ARB in patients with relatively good early graft function[20]. Similar results were observed by Jennings et al[21] that were analyzed the safety of ACE inhibitors or ARB use within first eight to twelve weeks after transplantation. Consequently there is an increasing tendency of ACE inhibitors or ARB initiation prescription last decade[22].

These observations are important considering the »positive« effects of ACE inhibitors or ARB. Namely, ARB and ACE inhibitors may prevent heart failure in patients with left ventricular dysfunction and may favour the regression of left ventricular hypertrophy (LVH). These effects are important due to the fact that a great majority of patients who undergo renal transplantation already have LVH and a certain degree of left ventricular dysfunction because of the well known consequences of End-Stage-renal disease and maintains dialysis[2,13]. Furthermore, they have a protective role in atherosclerosis development that is important because cardiovascular diseases are the main cause of increased morbidity and

mortality in RTRs[1]. Namely, according to the study by Cieciura et al[23] ACE inhibitors or ARB in RTRs can prevent an increase in the thickening of the intima-media complex of the carotid artery. And additional benefits of these drugs are their antiproteinuric effect and improvement of post-transplantation eritrocytosis[2,4].

In present study the most of our patients required a combination of antihypertensive drugs and only small proportion of them, in both groups, achieved the target blood pressure (<130/80 mmHg) after one-year of follow up. These results are in accordance with the previous reports that showed that in majority of RTRs the pharmacological treatment is often based on combination of two or more antihypertensive drugs and in most studies only 17–35% of RTRs achieved the target blood pressure values. Pointing that a more »aggressive« approach for the management of hypertension in this population of patients is needed.

Therefore, according to experience from our Institution early initiation of ACE inhibitors or ARB appears to be safe in carefully selected recipients with relatively good early graft function. Recipients with a good graft function may benefit from their early use due to their numerous positive effects. The introduction of ACE inhibitors or ARB as a part of antihypertensive therapy in RTRs especially in early post-transplantation period requires frequent and careful monitoring of these patients.

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L. Orlić
Department of Nephrology and Dialysis, Division of Internal medicine, University Hospital Rijeka, 51000 Rijeka, Croatia
e-mail: lidija.orlic@ri.t-com.hr

UPOTREBA ANGIOTENZIN INHIBITORA I BLOKATORA ANGIOTENZINSKIH RECEPTORA U RANOM PERIODU NAKON TRANSPLANTACIJE BUBREGA

SAŽETAK

Prema sadašnjim preporukama upotreba inhibitora angiotenzin konvertirajućeg enzima (ACE inhibitor) ili blokatora angiotenzinskih receptora (ARB) u primatelja bubrežnog transplantata nije preporučljiva u ranom periodu nakon transplantacije. Cilj ovog rada je procijeniti učinkovitost i sigurnost rane primjene (u prvih šest mjeseci nakon transplantacije) u odnosu na kasnu primjenu (nakon šest mjeseci od transplantacije) ACE inhibitora ili ARB-a. Ispitivanu skupinu činilo je 108 bolesnika sa bubrežnim transplantatom (50 muškaraca nad 58 žena) koji su u terapiji imali ACE inhibitor ili ARB u cilju kontrole krvnog tlaka. Primatelji su bili podijeljeni u dvije skupine, prema vremenu uvođenja

ACE inhibitora ili ARB-a. Ranu skupinu činili su bolesnici kod kojih su ACE inhibitor ili ARB uveden u toku prvih 6 mjeseci nakon transplantacije, a kasnu skupinu oni kojima su navedeni lijekovi uvedeni nakon 6 mjeseci od transplantacije. U svakog bolesnika analizirani su: serumske vrijednosti kreatinina, kalija i hemoglobina, na početku uvođenja terapije, te nakon jednog, tri, šest i dvanaest mjeseci. U 54 (50%) od 108 analiziranih bolesnika ACE inhibitori/ARB su uvedeni u prvih šest mjeseci nakon transplantacije, a u najvećem broju njih u prva tri mjeseca (90,7%). U dodatnih 54 (50%) bolesnika ACE inhibitori / ARB su uvedeni nakon šest mjeseci od transplantacije. Nije bilo statistički značajne razlike između dviju skupina obzirom na dob, spol i trajanje dijalize prije transplantacije. Analizirajući vrijednosti hemoglobina, serumskog kreatinina i kalija u navedenom vremenskom razdoblju nije bilo statistički značajne razlike između grupa, kao niti unutar iste grupe. Nakon 12 mjeseci praćenja ciljne vrijednosti krvnog tlaka postiglo je u prvoj skupini 14 (25,9%) bolesnika, a u drugoj 13 (24,1%) (p=NS). Prema našem iskustvu možemo zaključiti da je rana primjena ACE inhibitora ili ARB nakon transplantacije bubrega sigurna.