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Original Article

Renin–angiotensin–aldosterone system inhibitors lower hemoglobin and hematocrit only in renal transplant recipients with initially higher levels

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ABSTRACT

Aim: We have analyzed the effects of renin–angiotensin–aldosterone system (RAAS) inhibitors on evolution of hemoglobin (Hb) and hematocrit (Htc) levels as well as on the evaluation of kidney graft function in stable renal transplant recipients (RTRs) in respect with initially higher or lower Hb and Htc values.
Methods: The study group comprised of 270 RTRs with stable graft function. Besides other prescribed antihypertensive therapy, 169 of them have been taking RAAS inhibitors.
Results: We wanted to analyze the effect of the use of RAAS inhibitors on Hb and Htc in patients with initially higher or lower Hb/Htc values. For this analysis, only RTRs that were taking RAAS inhibitors were stratified into two groups: one with higher Hb and Htc (initial Hb ≥ 150 g/L and Htc ≥ 45%) and another one with lower Hb and Htc (initial Hb < 150 g/L and Htc < 45%) values. Thirty-four RTRs with initially higher Hb and 41 RTRs with initially higher Htc had a statistically significant decrease in Hb ($p = 0.006$) and Htc ($p < 0.0001$) levels after 12-months of follow-up. In the group of patients with initially lower Hb (135 RTRs) and Htc (128 RTRs) there was a significant increase in Hb ($p = 0.0001$) and Htc ($p = 0.004$) levels through the observed period. The use of RAAS inhibitors has been associated with a trend of slowing renal insufficiency in RTRs ($p = 0.03$).
Conclusion: RAAS inhibitors lower Hb and Htc only in RTRs with initially higher levels. In patients with initially lower Hb and Htc levels, the use of these drugs is followed by beneficial impact on erythropoiesis and kidney graft function.

1. Introduction

Kidney transplantation (TX) is considered to be the treatment of choice for patients with end-stage renal disease. Moreover, a successful kidney TX will correct not only the excretory functions of the kidney but also the endocrine functions [1]. Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor type 1 blockers (ARBs) are often prescribed for renal transplant recipients (RTRs). Renin–angiotensin–aldosterone system (RAAS) inhibitors are attractive medication after kidney TX due to their antihypertensive and antifibrogenic effects that may prevent chronic renal allograft dysfunction, potentially improving transplant survival. Blockade of the RAAS, leading to decreased glomerular hypertension and transforming growth factor-beta-induced collagen formation, can also have renoprotective effects. Furthermore, ACE-I and ARBs have been used to reduce red blood cells count in patients with posttransplant erythrocytosis (PTE) [2,3]. We [4] and others [5–7] have shown that ACE-I and ARBs are safe and effective therapy even in the early period after kidney TX. In nontransplant patients, blockade of the RAAS with ACE-I or ARBs has been shown to reduce proteinuria and delay the progression of chronic kidney disease (CKD). Because of their numerous well documented »positive« effects, these drugs are the most common prescribed antihypertensive in the general population [4,8]. Despite these potential benefits of RAAS inhibitors, controversy surrounds their usage in practice because of the concern of side effects, such as hyperkalemia, renal dysfunction and anemia. [3] However, the data about the association between anemia and the use of RAAS inhibitors in RTRs are conflicting. Some investigations report RAAS-inhibitors to be an independent predictor of anemia in RTRs, while others have not found such association [8].

According to these observations, we have analyzed the effects of ACE-I and ARBs on the evolution of hemoglobin (Hb) and hematocrit (Htc) levels in stable renal transplant patients in respect with initially

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higher or lower Hg and Htc values. We also wished to determine the effect of these agents on the evolution of kidney graft function, also in respect with initially higher or lower Hb and Htc values.

2. Methods

This was a retrospective observational study. The study group comprised of 270 RTRs (158 males) with stable graft function and mean age 53.5 ± 12.1 years. Stable graft function has been defined as a time interval of at least three months duration where complications, such as rejection crises, viral infections, acute tubular necrosis, surgical interventions and therapies with mono- or polyclonal antibodies, have been ruled out by clinical and laboratory findings. Patients with signs of acute or chronic bleeding, as well as those who have been receiving transfusion, iron and EPO therapy, have been excluded from this analysis. 13 patients received a kidney from a living related donor and 257 patients received a cadaveric kidney transplant. Dialysis treatment before transplantation lasted on average 42.9 ± 40.1 (range from 1 to 254) months. Most of the patients have been receiving induction therapy with IL-2 receptor blockers (daclizumab or basiliximab). As a maintenance therapy, most of them have been receiving calcineurin inhibitors (CNI), tacrolimus or cyclosporine, and mycophenolate mofetil or azathioprine, with or without a low dose of corticosteroids. Furthermore, as late maintenance therapy, mTOR inhibitors have been introduced in 11 patients due to CNI-nephrotoxicity or a history of malignancy. Patient's characteristics are shown in Tables 1A, 1B, 1C, 1D, 1E.

Beside other prescribed antihypertensive therapy, 85 of them have been taking ACE-I and 84 ARBs. On the other hand, 101 RTRs haven't been receiving a therapy with RAAS inhibitors. None of the analyzed patients have been treated with a combination of ACE inhibitors and ARBs. There were no patients with spironolakton.

Table 1B
Factors associated with Hb < 150 g/L in multivariate analysis (logistic regression).

	OR	95%CI	P value
Maintenance immunosuppression			
Tacrolimus	0.287	0.0774–1.0650	0.06
Cyclosporine	0.297	0.0834–1.0592	0.06
MMF	0.848	0.2007–3.5909	0.823
Azathioprine	0.365	0.0907–1.4753	0.157
Corticosteroid	0.446	0.1274–1.5625	0.206
Diuretic use	0.421	0.0453–3.9227	0.447
Diabetic nephropathy	1.141	0.3127–4.1694	0.841
Chronic GN	0.853	0.4362–1.6694	0.643

*Odds ratio (OR), confidence interval (CI), glomeluronephritis (GN).

We took the data on Hb, Htc, serum creatinine, potassium and medication from medical records. Glomerular filtration rate (GFR) was estimated according to the CKD-EPI formula. The data have been analyzed prior to ACE-I/ARBs introduction and at the end of the third, sixth and twelfth month. Immunosuppressive and antihypertensive therapy has been prescribed by nephrologists.

The primary endpoint of the study was to explore the association between the use of ACE-I, ARBs or no treatment with RAAS inhibitors and Hb, Htc, serum creatinine and potassium during the 12-month period of follow-up. Secondary endpoints were as following:

- to analyze the effect of the use of RAAS inhibitors (ACE-I or ARBs) on Hb, Htc, serum creatinine, GFR and potassium in all included patients
- to analyze the effect of the use of RAAS inhibitors on Hb and Htc in patients with initially higher or lower values. For this analysis, RTRs were stratified into two groups: one with higher Hb and Htc (initial Hb ≥ 150 g/L and Htc ≥ 45%) and another one with lower Hb and Htc (initial Hb < 150 g/L and Htc < 45%) values.

Table 1A
Demographic data of analyzed patients.

Total (n = 270)	ACE-I (n = 85)	ARB (n = 84)	Without therapy (n = 101)	p*	p**	p***
Age (years)	51.1 ± 13	54.6 ± 9.8	54.8 ± 12.6	NS	NS	NS
Gender (M:F)	49:38	46:38	63:38	NS	NS	NS
Duration of dialysis (months)	34.4 ± 40.3	50.4 ± 47.4	45.7 ± 41.2	NS	NS	NS
Dialysis modality						
HD, n (%)	76 (89.4%)	76 (90.5%)	89 (88.1%)	NS	NS	NS
PD, n (%)	9 (10.6%)	3 (3.6%)	11 (10.9%)	NS	NS	NS
HD/PD, n(%)	2 (2.4%)	5 (6%)	1 (1%)	NS	NS	NS
Etiology of CKD						
Diabetic nephropathy, n (%)	6 (7.1%)	8 (9.5%)	6 (5.9%)	NS	NS	NS
Nondiabetic nephropathy, n (%)	13 (15.3%)	8 (9.5%)	6 (5.9%)	NS	0.03	NS
Chronic GN, n (%)	39 (45.9%)	27 (32.1%)	30 (29.7%)	NS	0.03	NS
Polycystic kidney disease, n (%)	12 (14.1%)	12 (14.3%)	14 (13.9%)	NS	NS	NS
Chronic PN, n (%)	5 (5.9%)	12 (14.3%)	9 (8.9%)	NS	NS	NS
Chronic nephritis	4 (4.7%)	8 (9.5%)	12 (11.9%)	NS	NS	NS
Unknown, n (%)	6 (7.1%)	8 (9.5%)	18 (17.8%)	NS	0.02	NS
Other, n (%)	2 (2.4%)	1 (1.2%)	6 (5.9%)	NS	NS	NS
Hypertension, n (%)	82 (96.5%)	82 (97.6%)	87 (86.1%)	NS	NS	NS
Diabetes, n (%)	12 (14.1%)	18 (21.4%)	18 (17.8%)	NS	NS	NS
Dyslipidemia, n (%)	47 (55.3%)	45 (53.6%)	40 (39.6%)	NS	0.2	0.04
BB use, n (%)	35 (41.2%)	40 (47.6%)	41 (40.6%)	NS	NS	NS
CCB use, n (%)	36 (42.4%)	46 (54.8%)	40 (39.6%)	NS	NS	0.03
Diuretic use, n (%)	10 (11.8%)	23 (27.4%)	15 (14.9%)	0.009	NS	0.03
Maintenance immunosuppression						
Tacrolimus, n (%)	34 (40%)	43 (51.2%)	70 (69.3%)	NS	0.0001	0.009
Cyclosporine, n (%)	39 (45.9%)	34 (40.5%)	20 (19.8%)	NS	0.0001	0.002
MMF, n (%)	66 (77.6%)	75 (89.3%)	83 (82.2%)	NS	NS	NS
Azathioprine, n (%)	13 (15.3%)	8 (9.5%)	11 (10.9%)	NS	NS	NS
m-TOR inhibitors, n (%)	3 (3.5%)	7 (8.3%)	1 (1%)	NS	NS	0.02
Corticosteroid, n (%)	63 (74.1%)	76 (90.5%)	81 (80.2%)	0.005	NS	0.04

*Angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor type 1 blockers (ARBs), male (M), female (F), renal replacement therapy (RRT), hemodialysis (HD), peritoneal dialysis (PD), chronic kidney disease (CKD), glomerulonephritis (GN), pyelonephritis (PN), beta blockers (BB), calcium channel blockers (CCB); non-significant (NS).
p*—ACE-I vs. ARBs.
p**—ACE-I vs. without therapy.
p***—ARBs vs. without therapy.