Does Aliskiren Influence the Changes of Global Longitudinal Strain in Patients with Diastolic Dysfunction?

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Abstract: The aim of our study was to investigate the effects of Aliskiren on the blood pressure values as well as on the myocardial function, assessed by GLS (global longitudinal strain) in patients with uncontrolled AH (arterial hypertension) and diastolic dysfunction. Forty five nondiabetic patients (29 men and 16 women, mean age 58.7 ± 12.4 years) with BP (blood pressure) $> 140/90$ mm Hg despite of combined antihypertensive therapy (diuretic, calcium channel blockers, beta-blockers) were evaluated. All of them had echocardiographic data for diastolic dysfunction: E/E' ratio ≤ 8 , E/A ratio < 0.8 , DT (deceleration time) > 200 ms. Aliskiren 2×150 mg per day was added to the previous therapy. The follow-up period was 1 year, including monthly clinical visits. Echocardiographic assessment of the left ventricular function by longitudinal strain and Doppler analysis of the transmitral blood flow was performed at months 1, 6 and 12. The baseline mean measurements of systolic and diastolic BP values showed $(153.4 \pm 14.4)/(99.2 \pm 6.7)$ mmHg for males and $(157.6 \pm 12.5)/(97.3 \pm 8.2)$ mmHg for females. The systolic and diastolic BP values at the end of the 1st month were $(131.7 \pm 7.4)/(83.6 \pm 5.2)$ mmHg in men and $(132.4 \pm 5.3)/(81.8 \pm 6.9)$ mmHg in women ($P < 0.05$, compared to the initial BP values). The baseline ratio of E/E' was found to be 6.5 ± 0.9 , E/A— 0.6 ± 0.01 and DT— 258 ± 32.7 ms. The values of these parameters at month 12 were as follows: E/E'— 7.0 ± 0.64 , E/A— 0.7 ± 0.05 , DT— 239 ± 16.5 ms ($P = NS$). Baseline global longitudinal strain in men was $-10.4 \pm 0.7\%$ and $-11.0 \pm 0.9\%$ in women, whereas GLS at month 12 showed values of: $(-16.3 \pm 0.9\%)$ and $(-17.5 \pm 0.7\%)$ for males and females respectively ($P < 0.05$). During the whole period of treatment with Aliskiren and follow-up no adverse effects were registered. Aliskiren, added to a combined antihypertensive therapy (without RAAS—renin-angiotensin-aldosterone system blocker) in patients with uncontrolled AH and diastolic dysfunction provides not only a better BP control, but also a significant improvement of the myocardial function, assessed by global longitudinal strain. The 12 months treatment with Aliskiren was safe and well tolerated.

Key words: Aliskiren, arterial hypertension, diastolic dysfunction, global longitudinal strain.

1. Introduction

AH (arterial hypertension) is an important cardiovascular risk factor worldwide [1, 2]. Despite of the large choice of antihypertensive drugs, available nowadays, the control of AH is quite insufficient and the majority of hypertensive patients do not reach the target values of BP (blood pressure) [1-3]. The main classes of drugs at first choice for AH treatment are: inhibitors of ACE-I (angiotensin-converting enzyme),

ARB (angiotensin II type 1 receptor blockers), thiazide or thiazide-like diuretics, CCB (calcium channel blockers) and BB (beta blockers). All of them are suitable for initiation and continuation of AH therapy, alone or in combinations [4-6].

The DRI (direct renin inhibitors) are a new therapeutic option for hypertensive patients and Aliskiren is the only representative of this class, approved for clinical use so far [2, 3, 7, 8]. Their antihypertensive effect is due to a specific blockage of the catalytic center of renin which they bound to with high affinity. Thus, the first and rate-limiting stage of renin-angiotensin-aldosterone cascade is inhibited—the

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conversion of angiotensinogen into angiotensin I [2, 5, 9].

In patients with cardiovascular diseases, including AH, diagnostic approach includes noninvasive assessment of myocardial function to specify the degree of morphological changes occurring, therapeutic approach, early and long-term clinical prognosis [10-12].

Tissue Doppler echocardiography is an advanced method for assessment of myocardial function [10, 12]. This technique allows both visual and quantitative interpretation of regional tissue velocity, strain, displacement and acceleration throughout the cardiac cycle in one image. The term “echocardiographic strain” is used to describe the regional deformation occurring in the myocardium during the cardiac cycle (myocardial extension, shortening and thickening) [12, 13]. The high temporal and velocity resolution allows evaluation of rapid movements during the systolic and diastolic isovolumetric periods. Analysis of the isovolumetric velocity and acceleration characteristics during the global systolic and diastolic changes provides important data for the elastic and contractile properties of the myocardium. The image of the tissue movement, obtained from the integral of tissue velocity curve along the longitudinal axis, is presented as a time-dimensional color map of the myocardium movement during the cardiac cycle [11-13].

2. Materials and Methods

The aim of our study was to investigate the effects of Aliskiren on the blood pressure and myocardial function, assessed by global longitudinal strain in patients with uncontrolled arterial hypertension and diastolic dysfunction.

Forty five consecutive patients with essential arterial hypertension—29 males and 16 females, mean age 58.7 ± 12.4 (44-69 years) were evaluated in this prospective study. These patients had insufficient BP control ($> 140/90$ mmHg) according to the current guidelines despite of the combined antihypertensive

treatment, including some of the following classes antihypertensive drugs: ACE-I (inhibitors of the angiotensin-converting enzyme), ARB (angiotensin II type 1 receptor blockers), CCB (calcium channel blockers), BB (beta-blockers) and thiazide or thiazide-like diuretics. All patients had echocardiographic (Echo) data for diastolic dysfunction I degree according to EAE/ASE-criteria since 2009: E/E' ratio ≤ 8 , E/A ratio < 0.8 , DT > 200 ms. Patients' cardiovascular risk was assessed as mild to moderate according to the current ESC/ESH Guidelines for evaluation and treatment of arterial hypertension since 2009. The exclusion criteria were: high cardiovascular risk as well as patients with secondary hypertension. Aliskiren 2×150 mg per day was added to the ongoing therapy after exclusion of previous RAAS blocker. The follow-up period was 1 year, including monthly clinical visits.

The blood pressure of the non-dominant arm was measured with a validated aneroid sphygmomanometer in a seated position and after initial 15 min rest, three times with 5 min intervals between the measurements. The average value of the three BP measurements was used for the objectives of the study. Patients were inquired thoroughly for adverse effects of the Aliskiren treatment at each follow-up visit. Echocardiographic assessment of the left ventricular function by longitudinal strain in the grey scale and Doppler analysis of the transmitral blood flow was performed at months 1, 6 and 12. All patients signed informed consent form before inclusion into the study.

Statistical analysis of the data was conducted using statistical program SPSS (Statistical Program for Social Sciences) for Windows version 13.0. The following statistical methods were used:

Descriptive statistics: (1) mean, standard deviation, minimum, maximum; (2) frequency analysis (nominal and ranks)—absolute and relative frequencies (percentage).

Methods for hypotheses testing: (1) parametric—*T*-test; (2) non-parametric—chi-square or

Fisher's exact test; non-parametric K-related samples.

For all tests as a level of significance we accepted $P < 0.05$.

3. Results

Baseline SBP (systolic blood pressure) and DBP (diastolic blood pressure) values in patients, enrolled in the study, were as follows: 153.4 ± 14.4 (range 142-168)/ 99.2 ± 6.7 (range 93-104) mmHg in men and 157.6 ± 12.5 (range 147-172)/ 97.3 ± 8.2 (range 92-106) mmHg in women.

Adding Aliskiren to the ongoing antihypertensive therapy (excluding RAAS blocker) resulted in a significant decrease of SBP and DBP in the follow-up period. All patients achieved target levels of BP $< 140/90$ mmHg within the first month of follow-up— 131.7 ± 7.4 (range 126-138)/ 83.6 ± 5.2 (range 72-87) mmHg for males and 132.4 ± 5.3 (range

124-137)/ 81.8 ± 6.9 (range 71-86) mmHg for females, $P < 0.05$ compared to baseline (Figs. 1 and 2).

Baseline E/E' ratio was 6.5 ± 0.9 , its value after 6 months— 6.6 ± 0.7 and after 12 months— 7.0 ± 0.64 , $P = \text{NS}$ (Fig. 3).

Baseline E/A ratio was 0.6 ± 0.01 , its value after 6 months— 0.6 ± 0.04 and after 12 months— 0.7 ± 0.05 , $P = \text{NS}$ (Fig. 4).

Baseline mean values of DT index were 258.4 ± 32.7 msec, at the 6th month— 246.2 ± 22.4 ms and at the 12th month of follow-up— 239.0 ± 16.5 ms, $P = \text{NS}$ (Fig. 5).

Baseline echocardiographic strain in men was $(-10.4 \pm 0.7\%)$ and in women $(-11.0 \pm 0.9\%)$. The strain at the 6th month was $(-12.3 \pm 1.1\%)$ for males and $(-13.2 \pm 1.4\%)$ for females; $(-16.3 \pm 1.5\%)$ for males and $(-17.5 \pm 1.8\%)$ for females at the 12th month, $P < 0.05$ compared to baseline (Fig. 6).

Fig. 1 Average SBP and DBP of male patients at baseline and after 1 month of therapy with Aliskiren ($P < 0.05$).

Fig. 2 Average SBP and DBP of female patients at baseline and after 1 month of therapy with Aliskiren ($P < 0.05$).

Fig. 3 Mean values of the E/E' ratio assessed by Doppler-echo at inclusion in the study, at the 6th month and at the 12th month of follow-up ($P = \text{NS}$).

Fig. 4 Mean values of the E/A ratio assessed by Doppler-echo at inclusion in the study, at the 6th month and at the 12th month of follow-up ($P = \text{NS}$).

Fig. 5 Mean values of DT index at inclusion in the study, at the the 6th month and at the 12th month of follow-up ($P = \text{NS}$).

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Fig. 6 Mean values of tissue Doppler-echo cardiographic strain of patients at inclusion in the study, at the 6th month and at the 12th month of follow-up ($P < 0.05$).

Treatment with Aliskiren was well tolerated by all patients. For the period of clinical observation no side effects and patients discontinuation have been registered.

4. Discussion

A serious problem facing modern cardiology is inadequate compliance and persistence of the majority of patients on antihypertensive therapy [1, 2]. Some of the widely discussed reasons for this phenomenon are side effects of conventional antihypertensive medication, lack of adequate therapeutic response and adulterate contact between doctors and patients [1, 9]. In this setting, implementation of a new antihypertensive class of drugs is encouraging [14]. Aliskiren (Rasilez®) is a direct renin inhibitor whose effect is realized by binding with high affinity and specificity to the catalytic site of renin, thereby inhibiting the first rate-limiting step of the RAAS, namely the conversion of angiotensinogen to angiotensin I [7, 9]. Although a new agent, the therapeutic effects of Aliskiren were tested in many randomized clinical trials with a variety of indications. The study AGELESS proved the superiority of antihypertensive effect of Aliskiren compared to ramipril with a similar safety profile and significantly lower rates of cough as a side effect [2]. ALOFT

(Aliskiren Observation of Heart Failure Treatment) program provided strong evidence that Aliskiren could significantly reduce BNP and NT-proBNP levels in patients with heart failure on conventional therapy compared to placebo [3, 15, 16]. The effect of the direct renin inhibitor on morbidity and mortality has been studied in patients with heart failure ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE), compensated patients, hospitalized for an acute heart failure ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes), as well as in adults (APOLLO) [2]. It should be pointed out the important safety information for Aliskiren following interim results review from the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints). These results indicate a higher incidence of non-fatal strokes, renal complications (end stage renal disease), hyperkalemia and hypotension, when Aliskiren 300 mg/d was added to ACE-I or ARB in patients with diabetes and $\text{eGFR} \leq 60 \text{ mL/min/1.73 m}^2$. That is why the RAAS blockers were excluded before our study initiation [17].

Experimental animal models of myocardial infarction have shown that Aliskiren reduces left ventricular hypertrophy and has cardioprotective effects [2, 6]. Moreover, a beneficial effect on markers of systolic and diastolic function has been observed

even when the changes of BP were not significant [5, 6]. In our study, similar beneficial effect on diastolic function was not found, probably due to the short follow-up period. The most probable reason for the observed positive effects, discussed by other authors, is the inhibition of metalloproteinases through the RAAS inhibition. These facts will be interpreted much more adequate after the final analysis of the ASPIRE (Aliskiren Study in Post MI patients to reduce Remodeling) study results. A significant decrease in BNP (brain natriuretic peptide) and NT-proBNP (N-terminal prohormone of brain natriuretic peptide) in patients with HF (heart failure), as illustrated in the ALOFT study provides more evidence for the cardioprotective effect of Aliskiren [2].

Since no studies have investigated the effect of Aliskiren on patients with uncontrolled hypertension and diastolic dysfunction compared to combination therapy so far, we aimed to evaluate its effect on BP and on global myocardial function [18-20]. The Doppler-echo parameters of transmitral blood flow, specifying diastolic function, and the changes in myocardial function, revealed by global longitudinal strain assessment, were examined and followed-up.

Adding Aliskiren to antihypertensive therapy resulted in a significant decrease in SBP and DBP during the follow-up period. All patients achieved target levels of BP < 140/90 mmHg within the first month of follow-up— 131.7 ± 7.4 (range 126-138)/ 83.6 ± 5.2 (range 72-87) mmHg for men and 132.4 ± 5.3 (range 124-137)/ 81.8 ± 6.9 (range 71-86) mmHg for women. In all patients BP remained within the normal range during the follow-up of one year. It is essential that no side effects and adverse reactions were observed for this period in our group. Interestingly, although the changes in the parameters of diastolic dysfunction were statistically not significant, myocardial function assessed by echocardiographic longitudinal strain was reliably improved. In this setting our results are unidirectional with the data of the ALOFT study. The baseline GLS in men was $(-10.4 \pm$

$0.7\%)$, while in women $(-11.0 \pm 0.9\%)$. The strain at the 6th month was $(-12.3 \pm 1.1\%)$ and $(-13.2 \pm 1.4\%)$ for men and women respectively, while at the 12th month $(-16.3 \pm 1.5\%)$ and $(-17.5 \pm 1.8\%)$ ($P < 0.05$ compared to baseline). These findings pointed out that traditional Doppler-performance evaluation of diastolic function did not correlate with changes in global myocardial function. In this regard, echocardiographic longitudinal strain is a method with greater potential and prospects.

5. Conclusions

Aliskiren, added to a combined antihypertensive therapy (without RAAS blocker) in patients with uncontrolled AH and diastolic dysfunction provides not only a better BP control, but also a significant improvement of the myocardial function, assessed by global longitudinal strain. This study shows that the 12 months treatment with Aliskiren was safe and well tolerated. According to the literature data, GLS about -12% is in good correlation with systolic dysfunction and LVEF about 35% [21]. The baseline GLS values in our patients with diastolic dysfunction grade I and preserved global systolic function were similar. These data could be interpreted with caution, because of the subjectiveness—a major factor in the implementation of the methodology, as well as there are still no standardized normal values for GLS. Despite of the observed discrepancy, the important finding in our study was the statistically significant trend towards improvement of myocardial function, assessed by GLS, during the treatment with Aliskiren. Further studies with “hard” end-points (coronary events, morbidity and mortality rate) are needed to elucidate the role of this drug for cardioprotection and cardiovascular risk reduction.

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