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Effects of a short-term alirocumab administration on the aortic stiffness: preliminary results

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Arterial stiffness and wave reflections are widely used in observational studies to analyse the determinants of haemodynamic changes observed in various clinical conditions and to understand the pathogenesis of their cardiovascular complications. A large number of publications and several reviews documented the changes in arterial stiffness and wave reflections after various interventions, either non-pharmacological or pharmacological.[1–4] Recently , the Consensus Document on the ventricular-arterial coupling in cardiac disease,[5] recognized to pulse wave velocity (PWV) the role of most commonly used non-invasive method for studying the large artery stiffness defining it as a gold-standard. Furthermore, the document explored the meaning of arterial stiffness in heart failure and cardiovascular disease, considering extremely useful the analysis of the ventricular-arterial coupling in the assessment of therapy.

A recent systematic review including a meta-analysis of six studies that explored the effects of simvastatin, rosuvastatin, lovastatin and atorvastatin on PWV demonstrated a lower arterial PWV in treated patients in comparison with the placebo groups [standarized mean difference (SMD) = 2.31, 95% CI: 1.15–3.45, $P_{\text{heterogeneity}} = 0.07$, $I^2 = 93\%$] than concluding for a beneficial effect of statin therapy on arterial stiffness.[6] Alirocumab, a human monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy[7] and clearly reduced the plasma level of low density lipoprotein (LDL-C) after 24-month treatment.[8] The aim of this preliminary clinical experience was to analyze the time-course of the changing in arterial stiffness in high-risk cardiovascular patients after alirocumab administration.

Three consecutive patients started with alirocumab injection twice a month for non-obtaining target values of LDL-C (> 70 mg/dL) in recognized very high risk patients. All patients performed the plasma determination of LDL-C at baseline and after three-month. Arterial stiffness was assessed by measuring PWV and augmentation index (AIX) using the Sphygmocor applanation tonometer system (AtCor Medical, Itasca, Ilinois, USA), a non-invasive diagnostic tool for the clinical evaluation of central arterial pressure at baseline and after 1-month, 2-month, 3-month and finally six-month. The SphygmoCor XCEL System derives the central wave-shaped aortic pressure from the pulsations of the brachial artery cuffs. Waveform analysis provides key parameters that include central systolic pressure, central pulsation pressure, and arterial stiffness indices such as increased pressure and increase index. The increase in central systolic blood pressure and the increase indexes (Augmentation index) have been reported as indicators of cardiovascular risk. The velocity of the arterial pulse wave is detected by the carotid and femoral arterial impulses simultaneously measured in a non-invasive manner. The carotid pulse is measured through the tonometer while the femoral pulse is measured through the pulsations with a cuff placed around the thigh. PWV values in normal ranges depend on the age of the examined subjects, but can be considered within 9–10 m/s; obviously, an increase in the wave velocity of the carotid and femoral impulses indicates an increase in aortic stiffness, or damage to the target organ. Measurements performed on a supine patient, in a quiet environment, excluding smoking in the hour before the examination or having abused vasoactive substances (coffee), keeping intact its pharmacological therapy. The AIX was measured at the level of the carotid artery by obtaining ten high quality pulse wave measurements with automatic calculation of AIX using the manufacturer's proprietary software and after normalizing to a heart rate of 75 beats/min and represents the

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Table 1. Time-course of aortic stiffness parametrs after alirocumab administration.

	Baseline	1-month	2-month	3-month	6-month
PWV, m/s	13.07 ± 2.4	12.23 ± 2.14	12.1 ± 1.73	11.1 ± 0.94	10.5 ± 1.43*
Aix75	36% ± 2%	30.3% ± 3.5%	34.3% ± 5%	34.3% ± 2.3%	34% ± 8.5%
Central PP, mmHg	59.3 ± 14.2	51.3 ± 15.9	53.3 ± 20.1	51 ± 5.2	53 ± 19.3
Central SP, mmHg	135.7 ± 28.2	129 ± 25.7	134.6 ± 30.9	118.7 ± 9.7	119.7 ± 18.1
Brachial SP, mmHg	147.7 ± 31.5	142 ± 31.5	146.8 ± 37.9	130.7 ± 14.5	131 ± 12.5
Brachial PP, mmHg	72.7 ± 16.6	65 ± 19.5	65.7 ± 26	63.7 ± 9.8	65.7 ± 22.5

PWV: pulse wave velocity; Aix75: augmentation index; PP: pulse pressure; SP: systolic pressure. *P < 0.05.

pressure boost that is induced by the return of the reflected waves at the aorta. The LDL-C was not calculated by Friedwald formula, but dosed directly using an elimination/cathalasis method performed by Siemens, ADVIA Chemestry.

Continuous variables were expressed as mean ± SD, while discrete variables are presented as counts with percentages (%). Pearson's coefficient was employed to evaluate the correlation among the main variables (the measurements of PWV, Aug Index, Brachial and central systolic pressure/ central pulse pressure through three months) and LDL reduction. The *t*-test for paired data has been performed, all statistical tests were two-tailed, with *P*-value < 0.05 considered significant. All the analyses were performed by using the SPSS 20.0 for Windows (SPSS, IBM).

We enrolled a sample of three patients (two males) with coronary artery disease who were treated with alirocumab 75 mg subcutaneously twice/month. All the remaining therapy (aspirin, ACE-inhibitors, beta-blockers and loop-diuretics) were not changed during the study period. Two patients were also treated with atorvastastin 40 mg/ day and ezetemibe 10 mg/day but without obtaining the desiring LDL-target (< 70 mg/dL) for secondary prevention. One patient, really intolerant to statins and ezetimibe, underwent alirocumab treatment for secondary prevention according to the huge distance to the LDL-goal. Mean age was 71 ± 6.2 years. Mean total cholesterol (TC), high density lipoprotein (HDL), tryglicerides and LDL at baseline were respectively 186.3 ± 32.1 mg/dL, 53 ± 21.9 mg/dL, 140.3 ± 64.9 mg/dL and 166.3 ± 23.4 mg/dL. Mean TC, HDL, LDL and tryglicerides after 6-month of therapy with alirocumab was proved respectively to be 157.3 ± 17.8 mg/dL, 57 ± 26 mg/dL, 73.6 ± 15.5 mg/dL and 148.7 ± 55.5 mg/dL. The differences was only significant for the LDL cholesterol (P = 0.03). The analysis of PWV and the other parameters obtained by the non-invasive evaluation of aortic stiffness has been described in Table 1.

In conclusion, different methods are normally used for the non-invasive evaluation of arterial stiffness[9] and many drugs seemed to be effective for reducing the aortic stiffness.[10] The 2018 European Society of Cardiology Guidelines[11] underlined as a threshold of 10 m/s for PWV was reported as clinically correlated to an increased cardiovascular risk and data coming from a systematic meta-analysis the relative risk for all-cause mortality resulted 1.15 for an increase in 1 m/s.[12] This generating-hypothesis preliminary research experience demonstrated as alirocumab was effective in reducing, at 6-month follow-up, the main important parameter of arterial stiffness (PWV), probably following the previous results obtained with statins. In fact, the meta-analysis of Upala, *et al*.[6] clearly evidenced as 0.5–6 months of therapy with statins improved significantly the PWV value, underling that the effects on statins on reducing the inflammation, the cellular oxidation and the sympathetic neural activity might play a role together with the lowering activity on hypercholesterolemia. In mice treated with alirocumab and atorvastatin, alirocumab inhibits atherosclerosis, improved the plaque morphology and enhanced the effects of atorvastatin through the decreased number of adhering monocytes and the abundance of T cells[13] assessed by the reduced expression of adhesion molecule (ICAM-1) at immunochemistry. Finally, PCSK9 inhibitors seemed to interfere with vascular inflammation in atherogenesis considering that vascular smooth cells proved to produce higher amounts of PCSK9 as compared to endhotelial cells especially in an inflammatory state.[14] This preliminary report deserves future investigations about the possible role of PCSK9 inhibitors on the vascular cells inflammation and atherosclerosis.

Disclosures

The authors of this manuscript have no disclosures to declare.

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