Macedonian Pharmaceutical Bulletin, 66 (Suppl 1) 85 - 86 (2020)
Online ISSN 1857 - 8969
UDC: 615.272.4:616.153.915
DOI: 10.33320/maced.pharm.bull.2020.66.03.042
Short communication

Is there a place for rosuvastatin in the Lp(a) management?

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Introduction

Lipoprotein(a) [Lp(a)], an LDL-like particle, is an independent risk factor for cardiovascular disease (CVD). Recent studies indicate that people born with elevated Lp(a) may have a two-fold to four-fold increased risk of heart attacks and other serious CV events compared to people with low Lp(a) levels (Waldeyer et al., 2017). Clinical data points out that most people have Lp(a) levels in the range of 5 to 29 mg/dL, while the risk of CVD starts to rise at 30 mg/dL and more steeply at levels of 50 mg/dL.

While multiple studies have shown that Lp(a) is associated with elevated CVD risk, reducing Lp(a) has not yet proven to reduce CVD risk. Currently, there is no registered Lp(a)-targeted medicine. Treatment primarily includes niacin 1–3 g/day, while in extreme cases, LDL-apheresis. Literature data regarding the most widely used LDL-lowering drugs, HMG-CoA inhibitors/statins is controversial, showing (no) Lp(a) reduction, and even a slight increase (Tsimikas et al., 2019; Vavlukis et al., 2016). Among white JUPITER participants, Lp(a) was a significant determinant of residual risk, and relative risk reduction with rosuvastatin was similar among participants with high/low Lp(a) (Khera et al., 2014). The AIM-HIGH trial demonstrated that adding niacin to statin therapy reduces Lp(a) by 21%, but had no effect on CV events (Boden et al., 2011), while in the FATS study, Lp(a) was not associated with progression of atherosclerosis after statin therapy (Zhao et al., 2016). The aim of this study was to determine whether rosuvastatin has a potential role in regulation of increased Lp(a).

Materials and Methods

Adult outpatients without documented atherosclerotic CVD from the UKIM-University Clinic of Cardiology in Skopje were subjected to analysis (n=53, mean age 52.4±10.9 yrs; 34 (64.2%) females and 19 (35.8%) males). Of the 53 analyzed patients, 66% had hypertension, 22.6% diabetes, 50.9% pre-diabetes, 18.9% were smokers, 23.3% had positive family history for CVD and 63.2% had hyperlipidemia, without statistically significant gender differences. Mean EUROSCORE was 3.2±3.4% (intermediate risk), with males being in the high-risk category (5.0±3.8% *vs.* 2.3±2.7%, p=0.004); 11.8% females and 42.1% males were with high/or very high risk (p=0.027).

Of all patients, 81.1% had total cholesterol (TC) above 5 mmol/L at the study entry (no gender

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differences), while pre-treatment lipid profile was as follows: TC 5.9±1.3 mmol/L; LDL-C 3.6±1.3 mmol/L; HDL-C 1.4±0.4 mmol/L; TG 2.0±1.1 mmol/L; ApoA1 1.6±0.3 g/L; ApoB 1.4±0.4 g/L and Lp(a) 48.1±73.0 mg/dL (range 7-342 mg/dL). 24.5% of the patients had Lp(a) levels above 50 mg/dL. The patients were treated medium term with rosuvastatin 20 mg/day (up to 20 weeks), when post-treatment lipid profile, HbA1c and fasting blood glucose (FBG) were determined.

Data was collected from patients' records, physical examination and blood sampling. All parameters were measured by validated assays. Traditional risk-factors, calculated European System for Cardiac Operative Risk Evaluation Score (EUROSCORE), lipids and glycemic profile were analyzed as variables. Adequate indicators were statistically analyzed by Chi^2 test, pared sample t-test, Wilcoxon Signed Ranks test and correlations. Significance was determined at a level of <0.05.

Results and Discussion

Statistically significant decrease of TC, LDL-C, ApoB and TG was observed (mean difference as follows: -1.66±1.20 mmol/L, p=0.000; -1.23±2.48 mmol/L, p=0.001; -.041±.30 g/L, p=0.000; -.31±.76 mmol/L, p=0.004 respectively) after 20 weeks of treatment. However, statistically insignificant increase of mean Lp(a) level was observed (mean difference 5.07±44.73 mg/dL, p=ns) using pared sample statistics. Wilcoxon Signed Ranks test found 25 negative ranks (decrease after treatment), 23 positive ranks and 5 ties (p=ns). Even divided in two groups: normal Lp(a) (mean 18.95±12.85 mg/dL) and increased Lp(a) (defined as Lp(a) > 50 mg/dL i.e. 137.94±104.86 mg/dL), there was no statistically significant difference in both groups (28.93±53.69 mg/dL and 139.47±97.45 mg/dL, respectively, p=ns).

Furthermore, positive correlations for Lp(a) and: female gender (r=-.514; s<0.000); LDL-C (r=.320; p=0.019); ApoB (r=.275; p=0.038) and CRP (r=.275; p=0.047), before statin treatment, were observed. However, analysis of the correlations after treatment demonstrated preserved correlation for Lp(a) only with female gender (-.374; p=0.006), explained by the treatment effect on TC, LDL-C and ApoB, but not on Lp(a).

After 12-20 weeks of treatment, small, however, statistically significant increase of HbA1c was observed (6.07±0.92% and 6.30±0.90% respectively, p=0.005), with no statistically significant difference in FBG (6.26±3.04 mmol/L and 5.69±2.09 mmol/L, respectively, p=0.059). It must be emphasized that this data was generated from the total study group, where 22.6% of the patients had diabetes.

Conclusion

The current study demonstrated no correlation between lipid-impact of rosuvastatin and its Lp(a) effect. In addition, there was no consistency of medium term rosuvastatin treatment on Lp(a) in "statin naïve" patients.

References

Boden, W.E., Probstfield, J.L., Anderson, T., Chaitman, B.R., McBride, R., Teo, K., 2011. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N. Engl. J. Med. 365, 2255-2267.

Khera, A.V., Everett, B.M., Caulfield, M.P., Hantash, F.M., Ridker, P.M., Mora, S., 2014. Lp(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER trial. Circulation 129(6), 635–642.

Tsimikas, S., Gordts, P.L.S.M., Nora, C., Yeang, C., Witztum, J.L., 2019. Statin therapy increases lipoprotein(a) levels. Eur. Heart J. 0, 1-10.

Vavlukis, M., Mladenovska, K., Daka, A., Dimovski, A., Domazetovska, S., Kuzmanovska, S., Kedev, S., 2016. Effects of rosuvastatin versus atorvastatin, alone or in combination, on lipoprotein (a). Ann. Pharmacother. 50(8), 609-615.

Waldeyer, C., Makarova, N., Zeller, T., Brunner, F.J., Niiranen, T., Salomaa, V., Kee, F., 2017. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur. Heart J. 38(32), 2490–2498.

Zhao, X.Q., Phan, B.A., Davis, J., Boltz, S., Dowdy, A.A., Monick, E.A., 2016. Mortality reduction in patients treated with long-term intensive lipid therapy: 25-year follow-up of the Familial Atherosclerosis Treatment Study - Observational Study. J. Clin. Lipidol. 10(5), 1091–1097.