Comparison of the Effect of Statin Types on the Reduction of Lipid Profile and HS-CRP Inflammatory Marker in Diabetics with Dyslipidemia

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COMPARISON OF THE EFFECT OF STATIN TYPES ON THE REDUCTION OF LIPID PROFILE AND Hs-CRP INFLAMMATORY MARKER IN DIABETICS WITH DYSLIPIDEMIA

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ABSTRAK

Peningkatan petanda inflamasi C-reactive protein (Hs-CRP) terkait keberadaan risiko penyakit kardiovaskular. Statin merupakan golongan inhibitor HMG CoA reduktase yang menghambat biosintesis kolesterol dan memiliki efek pleiotropik sehingga bermanfaat mencegah kejadian kardivaskular. Semua statin memiliki mekanisme aksi yang sama namun memiliki perbedaan struktur kimia, profil farmakokinetika, dan efikasi penurunan konsentrasi lipid. Tujuan penelitian ini adalah membandingkan efek macam statin yaitu simvastatin dan atorvastatin dalam menurunkan profil lipid dan petanda inflamasi Hs-CRP pasien diabetes mellitus tipe 2 (DMT2) dengan dislipidemia. Dilakukan studi observasional prospektif kohort terhadap pasien DMT2 yang mendapatkan terapi simvastatin 20 mg (n = 11pasien) dan atorvastatin 10 mg (n = 7 pasien) selama 6 minggu. Efektivitas terapi statin diukur melalui pemeriksaan profil lipid (kolesterol total, LDL-C dan trigliserida) dan petanda inflamasi Hs-CRP pre dan post terapi. Setelah 6 minggu terapi, profil lipid dan petanda inflamasi Hs-CRP sebelum dan sesudah terapi kelompok pasien yang mendapatkan simvastatin maupun atorvastatin tidak menunjukkan perbedaan yang signifikan (p > 0,05). Tidak dijumpai pula adanya perbedaan yang signifikan pada penurunan profil lipid antara kedua kelompok. Namun pada pemeriksaan petanda inflamasi Hs-CRP, kelompok atorvastatin menunjukkan penurunan yang signifikan dibandingkan dengan atorvastatin (p < 0,05). Simpulan, tidak terdapat perbedaan penurunan profil lipid berupa kolesterol total, LDL-C dan trigliserida pada pasien yang mendapatkan terapi simvastatin 20 mg dengan atorvastatin 10 mg selama 6 minggu. Atorvastatin memberikan penurunan petanda inflamasi Hs-CRP lebih besar dibandingkan dengan simvastatin. ***(FMI 2015;51:86-90)***

Kata kunci: *simvastatin, atorvastatin, lipid, Hs-CRP, diabetes, dislipidemia*

ABSTRACT

Elevated inflammation marker C-reactive protein (CRP) is commonly associated with cardiovascular disease. Statins inhibit the enzyme HMG-CoA reductase, which is required for cholesterol biosynthesis and might also exert pleiotropic effects so that beneficial in the prevention of cardiovascular disease. All statins have the same mechanism of action but different in chemical structures, pharmacokinetic profiles, and lipid reducing efficacy. The objective of this study was to compare the efficacy of two statins, atorvastatin and simvastatin to reduce the lipid profiles and inflammation marker Hs-CRP in patient diabetes mellitus type 2 with dyslipidemic. This was a prospective cohort observational study of 18 diabetes dyslipidemia patient taking either simvastatin 20 mg (n = 11 patient) and atorvastatin 10 mg (n = 7 patient) for about 6 weeks. The efficacy of therapy measured by lipid profiles (total cholesterol, LDL-C and triglyceride) and inflammation marker Hs-CRP. After 6 weeks therapy, lipid profile and inflammation marker Hs-CRP pre and post therapy of either taking simvastatin 20 mg or atorvastatin 10 mg did not shown the significance different (p > 0.05). There were also no significance different in lipid profiles between the two groups. In the other hand, the inflammation marker Hs-CRP serum of atorvastatin group significantly decrease compared to simvastatin group (p < 0.05). In conclusion, there were no different in reducing lipid profiles (total cholesterol, LDL-C, and triglyceride) in either patient taking atorvastatin 10 mg or simvastatin 20 mg after six weeks therapy. Atorvastatin decrease the inflammation marker Hs-CRP serums better than simvastatin. ***(FMI 2015;51:86-90)***

Keywords: *simvastatin, atorvastatin, lipid, Hs-CRP, diabetes, dyslipidemia*

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INTRODUCTION

Diabetics have an increased risk of cardiovascular disease by 2-4 times higher compared to patients without diabetes. Dyslipidemia is a major factor underlying the increased risk and is characterized by the presence of elevated levels of triglycerides, reduced levels of HDL-C and LDL-C particles that are smaller, denser and more atherogenic (Kumar & Singh 2010). Atherosclerosis is a complex process that is characterized by a combination of excessive inflammatory reaction and fat accumulation. To determine the risk for cardio-

vascular disease inflammatory markers can be examined. CRP is an acute phase of protein levels in serum which showed inflammation in the patient's condition and are proatherogenic (Jialal et al 2004, Paffen & deMaat 2006).

Diabetic dyslipidemia treatment strategies based on NCEP-ATP III and ADA is a statin therapy, a class of lipid-lowering drugs HMG CoA reductase inhibitors that can inhibit cholesterol biosynthesis and has pleiotropic effects that inhibit inflammation and stabilize atherosclerotic plaques (Smith et al 2004). All statins have the same mechanism of action but have differences in terms of chemical structure, pharmacokinetic profile and efficacy in lowering lipid concentrations (Schachter 2005). Simvastatin (half-life 1-3 hours) is a statin that is still used widely in diabetic dyslipidemia in Indonesia. Some clinical trials indicate that there are new statins, such as atorvastatin (half-life 14 hours), which is more effective in lowering lipid profile in patients with diabetes as compared to simvastatin. This study aimed to compare the effect of statins, the simvastatin or atorvastatin to decreased lipid profile such as total cholesterol, triglycerides, and LDL-C and hs-CRP inflammatory markers in patients with diabetic dyslipidemia.

MATERIALS AND METHODS

Type 2 diabetes patients with dyslipidemia who seek treatment at one of the private practice physicians Medicine Endocrinology Consultants in Surabaya during the period May to August 2013 who met the inclusion criteria in the form of LDL cholesterol > 100 mg/dl and/or TG > 150 mg/dl as well as free or at least 2-3 weeks after acute inflammation. The method used for the measurement of research variables, among others LDL with homogenous method, enzymatic calorimetry (SEKISUI); TG with GPO-PAP method, enzymatic calorimetry; whereas CRP with high sensitive measurement method of immunoturbidimetry. Statistical analyses were used to determine differences in the profile of inflammatory markers (hs-CRP) before and after therapy, in which paired t-test was used. As for the difference decrease in inflammatory markers (hs-CRP) between the simvastatin and atorvastatin we used independent t-test.

RESULTS

During the four-month study we found 19 patients who met the inclusion criteria with one patient dropped out due to death. Demographic data showed that the age of patients with diabetes was most prevalent in the age range > 41-60 years, comprising 55.56%. Observation of other comorbidities profile showed that hypertension is a disease that is most often found accompanying the study sample, comprising 33.33%, followed by coronary heart disease (CHD), which was 18.18%.

Patients who met the inclusion criteria were measured for lipid profile and inflammatory markers Hs-CRP before treatment as baseline values. Lipid profile test results obtained from 18 patients showed that baseline value of total cholesterol levels in simvastatin group patients were distributed in two categories: desirable (45.5%) and borderline high (54.5%) with a mean of 193.27 mg/dl whereas atorvastatin group baseline value mostly were in the range of desirable (57.14%) with mean172.29 mg/dl. In LDL-C examination, the patient's baseline value in simvastatin group largely in the range of near optimal (63.6%) with a mean of 107.27 mg/dl while the atorvastatin group was mainly distributed baseline at 2 range, which was optimal (57.1%) and near optimal (42.9%) with a mean of 98.43 mg/dl.

After 6 weeks of therapy with atorvastatin or simvastatin changes were visible in the proportion of patients in total cholesterol, LDL-C and triglycerides. Total cholesterol levels of simvastatin treatment group experienced an increase in the number of patients who were in desirable range (72.7%) but some patients also belonged into the high range (18.2%), whereas patients with atorvastatin therapy showed decrease in the number of patients in desirable range (71.4%), and found patients with high range (14.3%). On examination the highest LDL levels simvastatin group were in the range of optimal and near optimal (36.4%) while the atorvastatin group had increased LDL in some patients so that the number of patients who were in the optimal range was decreasing (28.6%), and some patients were within the range of borderline high (14.3%) and high (14.3%). As for TG examination, simvastatin group who are in the high range (36.4%) experienced a decline in the number of patients and more patients were in the normal range (36.4%). Atorvastatin group had not obtained the category of patients with very high and more patients were in borderline high category (28.6%).

Based on the trend of changes in the lipid profile, statistical analysis of paired t-test on pre and post treatment data revealed that simvastatin group gives a decrease in total cholesterol and triglycerides as well as LDL-C levels, which were not statistically significant ($p > 0.05$). In atorvastatin group there was elevated levels of total cholesterol and LDL-C and decrease in TG levels, which were not statistically significant ($p > 0.05$). Furthermore, based on statistical analysis of independent t-est there were no significant differences in changes of lipid profile such as total cholesterol,

LDL, and TG between simvastatin and atorvastatin groups ($p > 0.05$).

To determine the risk of cardiovascular disease in diabetic patients with dyslipidemia, we examined the levels of the inflammatory marker of high sensitivity C-reactive protein (Hs-CRP). Based on the results of hs-CRP level, baseline values held by most of the simvastatin group of patients was at average risk range (1.0 to 3.0 mg/L) that was equal to 54.55% of the patients; while the atorvastatin group baseline value was largely at high risk range (> 3.0 mg/L) that is equal to 57.14%. After getting therapy for 6-8 weeks, Hs-CRP levels of patients receiving simvastatin therapy increased with the greatest number in the range of high risk (> 3.0 mg/L) is 63.64%. In patients after getting the highest atorvastatin therapy in high-risk range also in the amount of 71.43%, but the proportion was less. Statistical analysis of the paired t-test was to determine whether changes Hs-CRP levels pre and post therapy simvastatin or atorvastatin significantly. Statistical analysis showed that there was no significant difference between pre and post treatment in either simvastatin or atorvastatin group ($p > 0.05$). Further statistical analysis to determine differences in decreased levels of Hs-CRP between the simvastatin compared to atorvastatin group. There were significant differences in changes in Hs-CRP levels between the administration of simvastatin compared with atorvastatin ($p < 0.05$).

DISCUSSION

Epidemiological data show that in developing countries, most patients with diabetes are in productive age of between 40 to 60 years (Shaw et al 2010). Comorbid hypertension is commonly seen in diabetes and complications of diabetes itself with prevalence depending on the type of diabetes, age, obesity, and tribes/ethnic groups. Hypertension is a major risk factor belonged to the microvascular complications of cardiovascular disease and type 2 diabetes which is usually coexist with other cardio-metabolic risk factors such as dyslipidemia (ADA 2012). Patients with hypertension have a higher prevalence of high blood cholesterol and vice versa. The higher the blood pressure, the higher the risk of cardiovascular disease. Therefore, patients with concomitant hypertension and hypercholesterolemia conditions should be given aggressive therapy to reduce the risk of cardiovascular disease (NCEP-ATP III 2002).

Based on ATP III, diabetes is regarded as an equivalent condition in which the risk of coronary disease, cardiovascular disease becomes 2 to 3 times higher when compared to the general population. Type 2 diabetes patients generally experienced serum lipid and lipoprotein abnormalities are referred to as atherogenic dyslipidemia. This is one component of the metabolic syndrome and contributes to an increased risk of CHD in patients with diabetes (NCEP-ATP III 2002). Based on the literature, levels of LDL-C in diabetic patients is generally not higher than patients who did not have diabetes. But in an increasing number of diabetic condition LDL particles are smaller and dense (,small dense LDL) that are more atherogenic thus increasing the risk of cardiovascular disease (NCEP-ATP III, 2002). In this study, the presence of elevated levels of LDL-C and/or triglycerides that occur in these patients is generally followed by an increase in total cholesterol levels. No significant change is likely due to large variations in the respective data levels lipid profile. Absence of significant differences in changes in lipid profile such as total cholesterol, LDL, and TG between the simvastatin compared with atorvastatin may be due to differences in the number of study subjects in which the atorvastatin group compared with simvastatin less so that it does not look statistically significance.

Statins are structural analogues of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) which would inhibit the synthesis of mevalonate, so there was no cholesterol biosynthesis. Barriers in cholesterol synthesis resulted in the upregulation of LDL receptors so that the effect will be an increase in catabolic rate of LDL fraction and extraction of the precursor liver LDL (VLDL remnant) from the blood, which causes a decrease in LDL (Malloy & Kane 2007). A number of studies indicate the effects of several drugs known as statins to decrease triglyceride levels significantly although less potent. Inhibited VLDL apolipoprotein B output from the liver allows the decrease of TG levels. Such constraints lead to a decrease in VLDL-triglserida amount that goes into circulation. Increased LPL activity that mediate the hydrolysis of VLDL-triglycerides, through the reduction of apoprotein CIII, which is a apolipoprotien that can inhibit the activity of LPL, will also reduce VLDL-triglyceride levels. The increase of TG-rich VLDL clearance was contribute by upregulation of LDL receptors. However, if the value of baseline triglyceride levels below 250 mg/dL, then a decrease in triglyceride levels do not exceed 25% of which are not dependent on the dosage and type of statin used (Stein et al 1998).

On the condition of diabetes mellitus type 2 insulin resistance, the condition of hyperglycemia and fatty acid release berlebihmenyebabkan metabolic changes in endothelial cells. Heksosamin pathway activation may mediate an increase in gene transcription of proinflammatory cytokines. Atherosclerosis is a complex process that is characterized by a combination

of excessive inflammatory reaction and fat accumulation. Inflammatory reaction caused by the activation of transcription factors such as nuclear factor-κβ (NF-κβ) and activator protein 1 that will induce the expression of inflammatory genes, by releasing chemokines, increase the production of inflammatory cytokines and increased expression of cell adhesion molecules (Beckman et al 2002). CRP is an acute phase reactant that acts as a marker of vascular inflammation and is directly involved in the inflammatory process. A number of studies have shown that elevated levels of CRP can predict the risk of cardiovascular diseases such as myocardial infarction (Lam et al 2006).

Benefits of statins not only on the cholesterol-lowering effect, but also through the mechanism of cholesterol-independent form pleiotropic effects that include increased endothelial function, increased NO bioavail-ability, reduced the incidence of vascular and myocard-ial remodeling, inhibiting vascular inflamma-tion and oxidation, and can stabilize atherosclerotic plaque (Davignon 2004, Zhou & Liao 2010). Mechanisms underlying the pleiotropic effects of this is the conversion of HMG-CoA barrier to acid L-mevalonate, statins also inhibit the synthesis of isopren-oid, such as farnesylpyrophosphate (FPP) and geranyl-geranylpyro-phosphate (GGPP) which is the mechanism downstream of mevalonate acid. The accumulation of Ras and Rho were inactive in the cytoplasm, it was caused by statins inhibit Ras and Rho isoprenilasi. Because Rho is the main target of the geranyl-geranylation, then the resistance of Rho and its downstream targets that Rho-kinase resulted in mechanisms that mediate the pleiotropic effects of statins on the vascular wall (Zhou & Liao 2010).

Statins can reduce systemic inflammation and vascular effectively by lowering the levels of hs-CRP in patients with hypercholesterolemia. CARE trial study results show that statins may decrease plasma levels of hs-CRP were significantly for more than 5 years in patients who did not experience recurrent coronary events. Based on the analysis and follow-up for 10 years of AF-CAPS/TexCAPS showed that hs-CRP levels decreased in patients with acute coronary event-free statin therapy. In addition, the data preeliminary of Pravastatin Inflammation/CRP Evaluation confirmed that statins can reduce levels of hs-CRP in primary and secondary prevention populations.

CONCLUSION

Atorvastatin 10 mg or simvastatin 20 mg after six weeks therapy produce similar result in reducing lipid profiles (total cholesterol, LDL-C, and triglyceride). Atorvas-tatin decreases the inflammation marker Hs-CRP serums better than simvastatin.

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