ANTIHYPERLIPIDEMIC AND PLEIOTROPIC BENEFITS OF WEEKLY USE OF ROSUVASTATIN IN PATIENTS WITH STATIN-RELATED ADVERSE EFFECTS

Orıgınal Artıcle

STATİN YAN ETKİSİ GELİŞEN OLGULARDA HAFTALIK ROSUVASTATİN KULLANIMININ ANTİHİPERLİPİDEMİK VE PLEİTROPİK ETKİNLİĞİ

Mustafa Karatas

GATA Haydarpaşa Training Hospital, Department of Internal Medicine

Hakan Terekeci

GATA Haydarpaşa Training Hospital, Department of Internal Medicine

Ahmet Uslu

GATA Haydarpaşa Training Hospital, Department of Internal Medicine

Yalcın Onem

GATA Haydarpaşa Training Hospital, Department of Internal Medicine

Emrah Turunç

Yeditepe University , Department of Internal Medicine

Cagatay Oktenli

GATA Haydarpaşa Training Hospital, Department of Internal Medicine

Corresponding Author
Yasar Kucukardali

Yeditepe University , Department of Internal Medicine Istanbul / Turkey
e-mail:yasarkardali@yahoo.com

ABSTRACT

There are limited data related antihyperlipidemic and pleiotropic benefits weekly use of statins in patients experiencing statin-related adverse effects.

Objective: This study examined the antihyperlipidemic and pleiotropic effects of weekly use of rosuvastatin in patients with statin-related adverse effects.

Methods: Patients experiencing statin-related adverse effects were included in this randomized controlled prospective study undertaken between 2008 and 2009. Rosuvastatin patients (n=22) received 10 mg of rosuvastatin weekly for 12 weeks, while control group (n=22) received no treatment. The following laboratory parameters were assessed at baseline and at week 12, blood lipids, alanin aminotransferase, creatinin kinase, P-selectin; mean platelet volume; E-selectin; tumor necrosis factor-α, and plasma interleukin-6.

Results: Rosuvastatin and control groups were similar with regard to mean age (50.4±17.7 vs. 53.7±14.5 y, respectively) and sex distribution. An increase in HDL-C, and a decrease in LDL-C and triglyceride levels were observed in the rosuvastatin group, while atherogenic dyslipidemia developed in controls. A significant difference was found between the two groups with regard to change in blood lipids from baseline to study end-point (p=0.023, 0.015, and 0.043, respectively). There were not found significant differences in pleiotropic efficacy parameters. Alanin

aninotransferase and creatinin kinase levels were improved in both groups.

Conclusion: Weekly use of rosuvastatin had beneficial effect impact on lipid profile and restored alanin aninotransferase and creatinin kinase levels to normal. However, no benefit with regard to pleiotropic effects was detected. Further studies with a larger sample size and long duration are needed to evaluate on pleiotropic effects.

Keywords: *weekly use of statins; rosuvastatin; antihyperlipidemic; pleiotropic effect.*

ÖZET

Statine bağlı yan etki gelişen olgularda haftalık statin kullanılması ile ilgili literatür oldukça azdır.

Amaç: Bu çalışmada statine bağlı yan etki gelişen olgularda haftada bir kez rosuvastatin kullanımının antihiperlipikemik ve pleotopik etkileri araştırılmıştır.

Metod: Randomize kontrollü prospektif çalışmadır. GATA Haydarpaşa Eğitim Hastanesinde 2008-2009 tarihleri arasında yapılmıştır. Statine bağlı yan etki gelişen olgular alınmıştır. Rosuvastatin grubuna (22olgu) haftada 10 mg ilaç ,12 hafta süreyle verilmiş, kontrol grubuna (22 olgu) ilaç verilmemiştir. Çalışmanın başlangıcında ve 12. haftada lipid düzeyleri, ALT, CPK, P-selektin, ve ortalama platelet volumü E-selektin, hs-CRP ,TNF-α ve IL-6 plazma düzeyleri ölçülmüştür.

Sonuçlar : Rosuvastatin ve kontrol grubunda yaş ortalamasında fark yoktur (50,4±17,7 vs 53.7±14.5). Cinsiyet dağılında fark yoktur. Rosuvastatin grubunda HDL-K artmış, LDL-K, TG azalmış, kontrol grubunda aterojenik dislipidemi gelişmiştir. Gruplarda tedavi öncesi ve sonrasında lipid parametrelerinda farklar anlamlı bulunmuştur (sırasıyla p:0.023, 0,015, 0,043). 12. haftada P-selektin düzeyi kontrol grubundan daha düşük bulunmuştur (p:0.035). Diğer plaetropik etkinlik parametrelerinde gruplar arasında fark yoktur. ALT ve CPK düzeyleri heriki grupta da gerilemiştir. Özet olarak aralıklı rosuvastatin kullanma ile lipid profili olumsuz yönde etkilenmemiş, tedavi ile erişilen düzey korunmuş, aynı zamanda ALT ve CPK yüksekliği normal sınırlara gerilemiştir. Ancak pleiotropik etkiler bakımından fayda sağlanmamıştır. Daha fazla olgu sayısı ile pleotropik etki konusunda daha açık bilgiler elde edilebilir.

Anahtar Kelimeler: *İntermittant statin; yanetki, rosuvastatin;antihiperlipidemi; pleotropik etki.*

INTRODUCTION

Although diet and lifestyle modification are the mainstays of hyperlipidemia treatment, their effect is usually limited and lipid-lowering medications are frequently required. Among these agents, statins have the greatest effect in terms of mortality and morbidity reduction, with a relatively superior safety profile (1,2). Main clinical adverse effects of statins include myalgia, myopathy, hepatotoxicity, rhabdomyolysis and drug interactions (3).

In clinical studies, statins have shown to exhibit other effects beyond cholesterol lowering, which are referred to as "pleiotropic effects" and that also include improved endothelial function, increased bioavailability of nitric oxide (NO), anti-inflammatory effects, plaque stabilization, endothelial progenitor cell stimulation, immunosuppression and other effects (4).

In the case of statin related side effects it is recommended that patients undergo: creatinin kinase measurements and monitoring, statin dosage reduction, discontinuation and rechallenge and alternate – day therapy(5). Because of the non lipid benefits of statin we believe

that continuation of statin can provide cardiovascular protective effect. There is some data support this hypothesis (6,7). In this manner chose of the proper statin is important. Lipophilic drugs must undergo hepatic metabolism to become hydrophilic and these reactions are catalyzed primarly by the cytochrome P450 superfamily of enzyme (8).

Concomitant use of statins with medications metabolized through hepatic P-450 enzymes is known to increase the risk of myopathy, therefore, myopathy may be related to an interaction between statins and this enzyme system (9). Rosuvastatin is a hydrophilic statin and it is not metabolized through hepatic P450 enzymes and half life is long. So it seems to have more advantages for rechallenge and alternate day therapy.

Mounting data suggest that statin monoterapy or statin based treatment are safe in patients with non alcoholic fatty liver deseases (NAFLD) and can improve liver tests and same time reduce cardiovascular diseases morbidity and mortality. These findings suggest that with statins we are able to get two birds with one stone (10).

Eleveted transaminase levels and NAFLD are not contraindications to statin use (11), and statins don't worsen liver function in most patients with chronic liver diseases (12).

In this study, antihyperlipidemic and pleiotropic effects of a single weekly dose (10 mg) of rosuvastatin for 12 weeks were examined in a group of patients who required a dose reduction or discontinuation of statin treatment due to adverse effects.

MATERIALS AND METHODS

The study was conducted at the the GATA Haydarpasa Training Hospital, Departments of Internal Medicine and Cardiology from September 2008 to June 2009 in hyperlipidemic patients. A total of 72 subjects between 23 and 80 years of age with myalgia, myopathy and elevated liver enzymes during statin treatment for hyperlipidemia were recruited.

Of these patients, adverse effects could not be directly attributed to the medication use in 18 patients, and 10 patients did not wish to participate. The remaining 44 patients were randomly assigned in two groups using 'Quickcalcs graph pad' software. Myalgia, increased alanine aminotransferase (ALT) and increased creatine phosphokinase (CPK) were detected in 2, 9, and 11 subjects in the rosuvastatin group, respectively. Corresponding figures were 2, 10, and 10 among control subjects. The study design is shown in **Figure 1.**

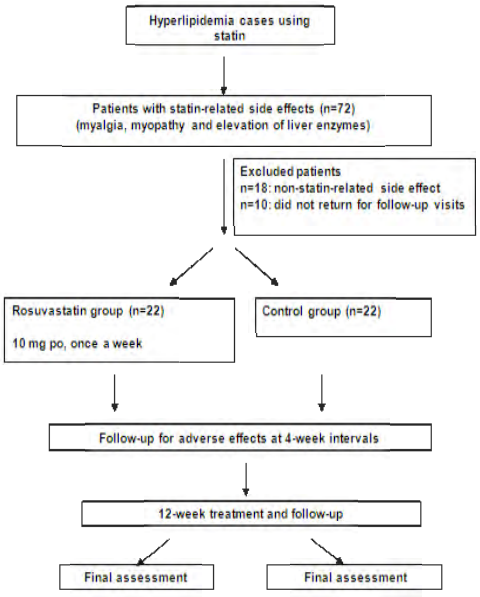

Figure 1. *Study diagram* **.**

Patients in the rosuvastatin group (n=22; 11 male, 11 female) received once weekly rosuvastatin (10 mg) for 12 weeks, while the control group (n=22; 9 male, 13 female) were not given any antihyperlipidemic agent. Patients were asked to continue their usual diets. But

they couldn't be monitored. All patients prior to enrollment in the study on rosuvastatin or other statins were taking same average dose statin. Patients were not washed out prior to randomization. The time interval between the last doses of their statin prior to randomization was similar. Concomitant medications were same for each group. Blood samples were obtained at baseline (Week 0) and at the end of study (Week 12). All patients completed the 12-week study.

INCLUSION CRITERIA

Recent use of statins within the past 3-month period, documented adverse effects due to statin use including myalgia, increased CPK (> 1 to 5 times the upper limit of normal), increased liver transaminases (> 1 to 5 times the upper limit of normal). Myalgia means "muscle pain" and is a symptom of many diseases and disorders. Myopathy is a muscle disease unrelated to any disorder of innervation or neuromuscular junction. CPK elevation may occur 1-5 fold.

EXCLUSION CRITERIA

Presence of acute infection at the time of blood sampling, inflammatory diseases, malignancy, rheumatic diseases, alcohol or substance abuse, psychiatric conditions requiring medical treatment, cognitive disorders.

DISCONTINUATION CRITERIA

Patient unwilling to continue, higher than 5-fold increase in transaminase and creatine phosphokinase levels as assessed with 4-week intervals.

Before study procedures were commenced, ethics committee approval was obtained.

BLOOD SAMPLİNG AND THE LABORATORY ANALYSES

Study-specific and routine tests were performed in GATA HEH Biochemistry Laboratory. Blood samples were obtained from the anticubital vein following 12 hours of fasting for ALT, CPK, total cholesterol (TC), low density lipoprotein – cholesterol (LDL-C), High density lipoprotein – cholesterol (HDL-C) and triglycerides (TG).

For the evaluation of pleiotropic effects, venous blood sampling from anticubital vein was done at baseline (Week 0) and at the end of study (Week 12) following 12 hours of fasting to assess the change in platelet function (P-selectin and mean platelet volume), endothelial function (E-selectin), and inflammatory status (TNF-alpha, and IL-6).

IL-6, TNF-α, E-selectin and P-selectin assays were performed using Invitrogen, ASSAYPRO, BENDER MEDSYSTEM (reference range: 21-186 ng/ml), and BENDER MEDYSTEM ELISA kits (reference range: 67-233 ng/ml), respectively.

STATISTICAL METHODS

Data analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows (version 15.0). Data are expressed as number, percentage, mean, median, and standard deviation. Between-group comparisons were performed using Mann-Whitney U test for continuous variables and chi-square for categorical variables. Within-group comparisons were performed using Wilcoxon signed-rank test, and Spearmen's correlation test was used for the assessment of correlations. A p value less than 0.05 was considered indication of statistical significance.

RESULTS

Among a total of 72 subjects 44 cases (20 male, 24 female , mean age 52 ±24 yr) were eligible for the study. There

were no significant differences between rosuvastatin and control groups at baseline characteristics with regard to age, gender, and laboratory parameters (**Table 1**).

Parameter	Rosuvastatin group	Control group	P
Sex (M/F) *	50%/50%, 11/11	41%/59%, 9/13	NS (p=0.54)
Age (yr)	50.40±17.74	53.77±14.53	NS (p=0.614)
TOTAL C (mg/dl)	238.05 ± 25.12	231.23±14.96	NS (p=0.344)
HDL-C (mg/dl)	46.09±16.19	47.95±10.68	NS (p=0.27)
LDL-C (mg/dl)	155.81±55.9	138.81±10.39	NS (p=0.23)
TG (mg/dl)	181.59±84.65	158.31±55.74	NS (P=0.25)
ALT (U /L)	61.90±49.53	58.09±37.69	NS (p=0.92)
CPK (U /L)	171.52±97.89	141.22±68.52	NS (p=0.29)
E-selectin (ng/ml)	54.00±13.03	58.72±13.03	NS (p=0.59)
P-selectin (ng/ml)	116.72±35.95	131.59±30.09	NS (p=0.25)
IL-6 (pg/ml)	58.72 ±18.19	64.68 ±16.76	NS (p=0.21)
TNF-α (pg/ml)	23.45±8.03	26.31±10.46	NS (p=0.46)
MPV (fL)	8.35±0.91	8.01±0.83	NS (p=0.47)

ALT: Alanine aminotransferase 11-55 U/L, CK Total: Creatine Kinase Total: 40-250 U/L, Cholesterol total: <200 mg/dL, Triglycerides (TG) <150 mg/dL, LDL-C: 62-130 mg /dl, HDL-C: 35-135 mg /dl

*Chi-square test, NS, not significant (p>0.05)

Table 1: *Comparison of rosuvastatin and control groups at baseline (Week 0.)*

Study parameters for rosuvastatin patients at baseline and at the end of the study are shown in **Table 2**.

Parameter	Baseline	Week 12	P*
TOTAL -C	238.05 ± 25.12	232.45±19.46	NS (p=0.36)
HDL-C (mg/dl)	46.09±16.19	47.13±15.39	NS (p=0.26)
LDL-C (mg/dl)	155.81±55.9	151.09±38.88	NS (p=0.35)
TG (mg/dl)	181.59±84.65	170.00±89.93	NS (p=0.72)
ALT (mg /dl)	61.90±49.53	36.81±19.05	p=0.002
CPK (mg /dl)	171.52±97.89	116.90±58.85	p=0.001
E-selectin (ng/ml)	54.00±13.03	58.86±11.04	NS (p=0.6)
P-selectin (ng/ml)	116.72±35.95	132.00±50.49	NS (P=0.07)
IL-6 (pg/ml)	58.72 ±18.19	65.22±15.10	NS (p=0.33)
TNF-α (pg/ml)	23.45±8.03	23.86±8.03	NS (p=0.87)
MPV (fL)	8.35±0.91	8.15±0.85	NS (p=0.47)

ALT: Alanine aminotransferase 11-55 U/L, CK Total: Creatine Kinase, Total: 40-250 U/L, Cholesterol, total: <200 mg/dL, Triglycerides (TG): <150 mg/dL, LDL-C: 62-130 mg /dl, HDL-C: 35-135 mg /dl

NS, not significant (p>0.05)

Table 2: *Comparison of parameters at baseline and at Week 12 in the rosuvastatin group.*

At week 12, ALT and CPK levels were significantly lower compared to baseline ($p < 0.05$). There were no differences biologic markers of pleitropic effects between groups.

Table 3 shows the changes in study parameters in the control group from baseline to the end of study. LDL-C and TG levels were significantly increased whereas ALT and CPK levels were significantly decreased after 12 weeks ($p<0.05$).

Parameter	Baseline	Week12	P
TOTAL –C (mg /dl)	231.23±14.96	240.23 ±21.57	P=0.055
HDL-C (mg/dl)	47.95±10.68	45.63±10.39	P=0.05
LDL-C (mg/dl)	138.81±10.39	161.81±29.01	P=0.018
TG (mg/dl)	158.31±55.74	189.72±62.80	P=0.004
ALT (U/L)	58.09±37.69	35.68±19.36	p=0.004
CPK (U/L)	141.22±68.52	39.04±32.09	p=0.002
E-selectin (ng/ml)	58.72±13.03	60.04±23.80	NS (p=0.06)
P-selectin (ng/ml)	131.59±30.09	195.81±49.34	NS (p=0.26)
IL-6 (pg/ml)	64.68 ±16.76	65.59±20.74	NS (p=0.91)
TNF-α (pg/ml)	26.31±10.46	37.72±30.82	NS (p=0.31)
MPV (fL)	8.01±0.83	8.10±0.88	NS (p=0.68)

ALT: Alanine aminotransferase 11-55 U/L, CK, Total: Creatine Kinase, Total: 40-250 U/L, Cholesterol, total: <200 mg/dL, Triglycerides (TG) <150 mg/dL, LDL-C: 62-130 mg /dl, HDL-C: 35-135 mg /dl

NS, not significant (p>0.05)

Table 3: *Comparison of parameters at baseline and at Week 12 in the control group.*

The differences in the change of laboratory parameters between rosuvastatin and control groups are shown in (**Table 4).**

Parameter	Rosuvastatin group Difference from baseline	Control group Difference from baseline	P
TOTAL -C	-5.60	+9.00	p=0.042
HDL-C (mg/dl)	+1.04	-2.31	p=0.023
LDL-C (mg/dl)	-4.72	+23.00	p=0.015
TG (mg/dl)	-11.59	+31.41	p=0.043
ALT (U/L)	-25.00	-22.40	NS (p=1.00)
CPK (U/L)	-54.31	-42.18	NS (p=0.91)
E-selectin (ng/ml)	+4.86	+1.22	NS (p=0.68)
P-selectin (ng/ml)	+15.28	+24.22	NS (p=0.21)
IL-6 (pg/ml)	+6.50	+0.90	NS (p=0.47)
TNF-α (pg/ml)	+0.41	+11.40	NS (p=0.43)
MPV (fL)	0.19	-0.86	NS (p=0.66)

NS, not significant (p>0.05)

Table 4: *Differences between rosuvastatin and control groups with regard to the change from baseline to the end of the study.*

A statistically significant difference was observed between the two groups with regard to the change from baseline to study end in the following parameters: TC (p=0.042), HDL-C (p=0.023), LDL-C (p=0.015), and TG (p=0.043). No new onset adverse effects were observed in the groups and all adverse effects resolved completely.

DISCUSSION

Intermittent use of statins is a novel treatment approach in high-risk patients or in subjects with treatment related side effects. In this study, single weekly dose of 10 mg of rosuvastatin have a beneficial effect on lipid profile, was able to maintain previously achieved blood lipid levels, and restored elevated ALT and CPK levels to normal. However, no benefit on pleiotropic effects was observed. In controls, despite normalization of ALT and CPK, previously achieved favorable blood lipid profile deteriorated. This was reflected in the significant difference between the groups at the end of study with regard to blood lipid levels in contrast to the lack of any difference in pleiotropic effects.

In some patients, statin treatment is discontinued due to adverse effects. Thus, some researchers have focused on alternative statin regimens (e.g. only several days a week) and examined their efficacy. In a study published in 2008, rosuvastatin given 2 days/week with daily doses between 5 and 10 mg for 8 weeks resulted in significant improvement of lipid profile (13). In this study 20% percent patients could not tolerate 2 days / week rosuvastatin, there was no control group and there was no randomization. In a similar study, it was shown that LDL-C levels were reduced by 48% and 39% in the once-daily and every-other-day groups, respectively without a major decrease in therapeutic benefit or increase in adverse events for a total duration of 12 weeks, in patients with hypercholesterolemia (14). Difference of this study from our study were lack of randomization and every-other day dose application. So, our study was the first of one which designed as a randomize, include control group and weekly dosage application. In contrast with two previous studies (13, 14), weekly rosuvastatin (10 mg) treatment was associated with a significant increase in HDL-C. Absence of atherogenic dyslipidemia in intermittent rosuvastatin group suggests preservation of the protective effect In our study, contrary to rosuvastatin group, control patients had atherogenic levels of dyslipidemia at the end of study.

Although the underlying mechanism remains unclear, it may result from changes in the lipid components of the hepatocyte membrane, leading to an increase in its permeability with a subsequent "leakage" of liver enzymes. In JUPITER trial, no significant differences was observed when the statin was compared with placebo (15). It is known that statin hepatotoxicity is frequently asymptomatic and usually resolves after

dose reduction or drug withdrawal (16). Base on the data we chosed rosuvastatin for weekly use and show safety of this drug on liver enzymes.

Statin-related myopathy may be influenced by genetics and tends to be dose-dependent. Ezetimibe can contribute to LDL-C reduction allowing a lower dose of statin to be used. Another approach is to administer rosuvastatin twice weekly (17). The long half-life of rosuvastatin along with its high potency make it a good candidate for weekly administration. While few studies have evaluated the efficacy of the described weekly statin therapy, the failure to address significant hyperlipidemia is associated with adverse health outcomes and costs (18). Weekly rosuvastatin use was shown well tolerated in patients intolerant of daily statin administration in present study.

There are limited data on pleiotropic effects of intermittent statin use and it is also related with hemodialysis patients. Intermittent doses of stain in hemodialysis patients proved to be as effective as the usual dose in reducing C-reactive protein levels and indicating an important reduction of the cardiovascular risk (19). In a sub-group study of MIRACL, Kinlay et al. examined a group of patients with acute coronary syndromes receiving aggressive atorvastatin treatment and, after 16 weeks of follow-up, detected a decrease in proinflammatory cytokines such as IL-6, serum amyloid A, P-selectin, E-selectin, soluble vascular cell adhesion molecule (SVCAM), sCD 40, and intercellular adhesion molecule-1 (20). Again in a subgroup analysis of MIRACL, the relationship between oxidised phospholipids, oxidised LDL-L, cardiovascular risk factors, and inflammatory biological markers was examined (21). Either no association or only a weak-association was found. In this study, we have attempted to address this issue. However, no significant benefits on these parameters were observed. Similarly, intermittent rosuvastatin use in our study was not associated with significant changes in IL-6 or TNF-α level.

Normal MPV is 4.5-8.5 fL (mean: 6.5 fL) (22) with higher volumes in young adults and children (23). In hypercholesterolemic patients, cholesterol content of the platelet is elevated and platelets become more sensitive to stimuli for platelet aggregation. Statins have been suggested to decrease thrombotic propensity via inhibition of platelet activation accompanied by hypercholesterolemia (24). Platelet activity is higher in subjects with elevated LDL-C compared to those without such elevation (25). The potential for platelet activation and aggregation, which play a major role in atherogenesis and thrombogenesis, can be monitored by MPV (22, 26).

Therefore, MPV was used to determine possible positive effect of the statin on inflammation and thrombotic processes in this study. Previously Broijersen et al. found decreased MPV with LDL-apheresis in 10 patients with familial hypercholesterolemia, without any effect of pravastatin on MPV (27). Mathur et al. examined MPV in a total of 94 patients attending to an emergency room and found increased MPV in those diagnosed with myocardial infarction or unstable angina compared to controls; however, there were no significant differences between statin users and non-users (28).

Despite absence of significant difference in MPV between the groups, at Week 12 a positive and strong (r=0.53) correlation with statistical significance (p=0.015) was detected between mean platelet volume and LDL-C in rosuvastatin patients in our study. This finding might be related to MPV lowering effect of LDL-C, which itself was slightly lowered by statin treatment.

Despite statistically significant relationships between the biomarkers such as TNF-α, IL-6, E-selectin, P-selectin, and MPV, no significant improvement in cytokine and biomarker levels were

detected from baseline to Week 12 in rosuvastatin patients compared to control subjects.

Potential limitations stil remain in our study. We did not perform power analysis for sample size calculations. Number of patients may be inadequate but we couldn't increase samle size due to financial limitations. So some results that lack of effect may be due to inadequate number of patients enrolled. The coefficient of variation for each assay couldn't provided.

CONCLUSION

In light of the significant reduction in the risk of life-threatening cardiovascular events that statins provide, primary care physicians should not withhold statin therapy from patients whose developed moderate side effect. Weekly dosage rosuvastatin with specific charactestics can provide safety administeration advantages for antihyperlypidemic effect but not pleiotropic effect. Studies with larger sample size may provide more information on pleiotropic effects of once-weekly rosuvastatin treatment.

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