The comparison of the effects of standard 20 mg atorvastatin daily and 20 mg atorvastatin every other day on serum LDL-cholesterol and high sensitive C-reactive protein levels

Gün aşırı 20 mg atorvastatin tedavisinin serum LDL-kolesterolü ve düksek duyarlı C-reaktif protein düzeyleri üzerine etkisinin günlük 20 mg atorvastatin tedavisi ile karşılaştırılması

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ABSTRACT

Objective: In this study, we aimed at comparing the effects of standard once daily 20 mg atorvastatin treatment with that of atorvastatin 20 mg administered every other day on serum lipids and high sensitive C-reactive protein (hs-CRP) levels.

Methods: Sixty-one patients with serum total cholesterol levels of above 200 mg/dl and low density lipoprotein (LDL) - cholesterol levels of above 130 mg/dl were included in this prospective, randomized study. The patients were randomized into daily treatment of 20 mg atorvastatin (standard treatment) and 20 mg atorvastatin every other day (every other day treatment) groups. Before the treatment and at each visit, serum lipids and hs-CRP levels of all the patients were measured. Statistical analyses were performed Chi-square, unpaired t and two-way repeated measurements ANOVA tests.

Results: In the every other day treatment group, there was a 36.1% reduction in LDL-cholesterol levels by the end of first month ($p<0.01$). At the end of three months there was further decrease of 10.2% in LDL-cholesterol levels when compared to 1 month levels ($p>0.05$). The LDL cholesterol levels of the group receiving 20 mg atorvastatin every day was reduced by %41 by the end of 1 month ($p<0.01$). At the end of three months, the difference between the changes in the all lipid parameters of the two groups was not found to be of statistical significance. In the group receiving the medication every other day, there was a 21% decrease in hs-CRP levels compared to the basal measurements at the end of first month ($p<0.05$). In the group, receiving the medication every day the decrease in hs-CRP levels at the end of one month was more striking (37%, $p<0.05$). However, the effects of both treatment arms on hs-CRP levels, did not differ significantly ($p>0.05$).

Conclusions: Alternate-day dosing of atorvastatin causes a significant lipid-lowering and antiinflammatory effects similar to that of daily administration and yet may provide some cost savings. *(Anadolu Kardiyol Derg 2008; 8: 407-12)*

Key words: Atherosclerosis, statins, atorvastatin, total cholesterol, low density lipoprotein cholesterol, hs-C reactive protein

ÖZET

Amaç: Bu çalışmada her gün alınan 20 mg atorvastatin tedavisi ile gün aşırı alınan 20 mg atorvastatin tedavisinin serum lipitleri ve yüksek duyarlı C-reaktif protein (CRP) düzeyleri üzerine etkilerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Bu prospektif randomize çalışmaya serum total kolesterolü 200 mg/dl, düşük yoğunluklu lipoprotein (LDL) kolesterolü ise 130 mg/dl'nin üzerinde olan 61 hasta alınmıştır. Hastalar günlük ve gün aşırı 20 mg atorvastatin alan iki gruba randomize edildiler. Tedavi öncesi ve her hastane gelişinde serum lipid parametreleri ve yüksek duyarlı CRP düzeyleri ölçüldü. İstatistiksel analizler Ki-kare, eşleştirilmemiş t ve iki-yönlü ANOVA testleri ile yapıldı.

Bulgular: Gün aşırı ilaç alan grupta birinci ayın sonunda LDL kolesterol düzeylerinde %36.1 azalma izlendi ($p<0.01$). Üçüncü ayın sonunda ise birinci aydaki değerlere göre %10.2 ek azalma izlendi ($p>0.05$). Her gün ilaç alan grupta ise birinci ayın sonunda LDL düzeylerinde %41 oranında

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azalma izlendi (p<0.01). Üçüncü ayın sonunda her iki grupta lipid parametrelerin değişimleri arasında istatistiksel olarak anlamlı bir fark yoktu. Gün aşırı ilaç alan grupta yüksek duyarlı CRP düzeylerinde 1. ayın sonunda %21 azalma vardı (p<0.05). Her gün ilaç alan grupta da yüksek duyarlı CRP düzeyleri belirgin oranda düştü (%37, p<0.05). Her iki tedavi grubunun yüksek duyarlı CRP düzeyleri üzerine olan olumlu etkileri arasında istatistiksel olarak anlamlı fark yoktu (p>0.05).

Sonuç: Gün aşırı alınan atorvastatin tedavisi daha az tedavi maliyeti ile birlikte standart günlük kullanım ile benzer lipid düşürücü ve antiinflamatuvar etkiler göstermiştir. *(Anadolu Kardiyol Derg 2008; 8: 407-12)*

Anahtar kelimeler: Ateroskleroz, statin, atorvastatin, total kolesterol, düşük yoğunluklu lipoprotein kolesterol, C-reaktif protein

Introduction

Elevation in the level of low-density lipoprotein (LDL) cholesterol is an important risk factor for the development and progression of atherosclerosis. The benefits of statins that reduce levels of LDL-cholesterol in primary and secondary prevention have been demonstrated by several randomized studies (1-3). Statins cause this benefit not only through their effects on lipids but also through their anti-inflammatory effects, which are believed to play an important role as well (4). Statins have also been shown to reduce high sensitive C-reactive protein (hs-CRP) level, which is an important risk predictor for myocardial infarction and stroke (5).

Today, statins are being used widely, having an important share in health expenses. Statin treatment administered every other day can result in a significant decrease in health expenses. Alternate-day dosing of statins may have role in lipid-lowering therapy in selected patients. Although previous studies conclude that alternate-dosing is an efficacious and safe alternative to daily dosing in lowering LDL-cholesterol (6-9), there is no data about the anti-inflammatory effect of alternate-day dosing of statins.

In this study, we aimed to compare the effects of standard once daily 20 mg atorvastatin treatment with that of atorvastatin 20 mg administered every other day on serum lipids and hs-CRP levels.

Methods

Sixty-one consecutive patients with serum total cholesterol levels >200 mg/dl and LDL- cholesterol levels >130 mg/dl who were considered as moderate to high risk according to National Cholesterol Education Program Expert Panel (NCEP-ATP III) (10) were included in this prospective, randomized study. The study protocol was approved by the institutional review board and informed consent was signed by all participants. Exclusion criteria were high levels of liver enzymes, diagnosis of acute coronary syndrome within the last 3 months, hospitalization due to any cause within the last three months, history of anti-lipemic use within the last 3 months and presence of infectious or inflammatory disease that might influence serum CRP levels.

The patients were randomized in 1:1 manner into 2 treatment groups: 1) 20 mg atorvastatin every other day (30 patients, group 1), or 2) daily treatment of 20 mg atorvastatin (31 patients, group 2). All study subjects received an individual instruction from a registered dietitian and followed an American Heart Association step II diet. Patients were requested to take their medication after dinner. Before the treatment, serum total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL) -cholesterol, triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine kinase levels of all patients were measured and recorded. Total cholesterol, HDL-cholesterol and triglycerides were assessed enzymatically by an autoanalyzer and LDL-cholesterol was calculated by the Friedewald formula (11). The hs-CRP level was determined using latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring). All the measurements were repeated at the end of first and third months of treatment. At each visit, the blood samples were drawn after an overnight fast. In the every other day treatment group, blood samples were obtained in the morning when the patient did not receive the pill. Compliance to treatment regimes was assessed by pill count at each visit. Patients were advised to report immediately any unusual muscle pain, weakness or brown urine. Safety and tolerability were evaluated throughout the study on the basis of adverse reporting, laboratory studies and physical findings. Weight and dietary adherence were assessed and documented at enrollment and each follow-up visit.

Statistical analysis

All statistical analyses were performed with SPSS version 13 (SPSS Inc., Chicago, Illinois, USA). Categorical variables were expressed as percentages and continuous variables as mean±SD. Comparison of categorical and continuous variables between groups was performed using the Chi-square test and unpaired t test, respectively. In comparison of measurable parameters within groups two-way repeated measurements ANOVA test (2:3 factorial design) was used. Tukey test was used as a post hoc analysis for multi-comparison of significant results. A p value of < 0.05 was accepted as statistically significant.

Results

Sixty-one consecutive patients (40 male, 21 female) with an average age of 55±11 years were included in this study. General features including age, gender, coronary heart disease and basal biochemical parameters of group 1 and group 2 were similar (Table 1).

In group 1, there was an approximately 28.3% reduction in total cholesterol levels by the end of first month (p<0.01) (Table 2). However, the total cholesterol levels at the end of third month were not significantly different than that of the first month (p>0.05). The LDL-cholesterol levels were also reduced by 36.1% by the end of first month (p<0.01). In contrast to the changes in the total cholesterol levels, there was a further 10.2% decrease in LDL-cholesterol levels at the end of third month compared to the first month levels (p>0.05) (Table 2 and Fig. 1). There was a

Table 1. Clinical and basal biochemical parameters of treatment groups

Parameters	Group-1 (n=30)	Group-2 (n=31)	p*
Age, years	53±13	57±11	NS
Men, %	60	67.7	NS
Hypertension, %	50	54.8	NS
DM, %	20	9.7	NS
Smoking, %	13.3	22.5	NS
CHD, %	10	19.3	NS
Total Cholesterol, mg/dl	244±26	242±29	NS
LDL-Cholesterol, mg/dl	166±25	162±23	NS
HDL-Cholesterol, mg/dl	45±7	47±12	NS
Triglyceride, mg/dl	163±64	159±55	NS
Hs-CRP, mg/L	4.33±5.62	6.91±5.88	NS

* - Chi-square test for comparison of categorical data and Student's t test – for comparison of continuous variables
Group 1 - treatment every other day
Group 2 - treatment every day
CHD- coronary heart disease, DM- diabetes mellitus, HDL- high-density lipoprotein, Hs-CRP- high sensitive C-reactive protein, HT- hypertension, LDL- low-density lipoprotein, NS- non-significant

42.7 % reduction in the LDL-cholesterol levels at the end of the third month therapy with 20 mg atorvastatin every other day compared to the basal levels (p<0.01) (Fig. 2). The changes in triglyceride and HDL-cholesterol levels are shown in Table 2.

Regarding the changes in the lipids parameters of the group receiving atorvastatin every day (Group 2), there was also a significant decrease (31.6%) in the total cholesterol levels by the end of first month (p<0.01) (Table 2). Similar to the group 1, there was no further decrease in the total cholesterol levels at the end of third month (p>0.05). The LDL cholesterol levels were reduced by 41% at the end of first month (p<0.01) (Table 2 and Fig. 1). However, there was no additional reduction in LDL cholesterol levels at the end of third month (p>0.05). The changes in the levels of HDL and triglycerides are shown in Table 2.

More strikingly, when we compared the changes in the lipid parameters at the end of the third month therapy between groups, there was no significant difference between the every day (group 2) and the every other day (group 1) treatment groups (Fig. 2, Table 2). In other words, 20 mg atorvastatin given either every day or every other day caused a similar decrease in the total cholesterol, LDL-cholesterol and triglyceride levels.

The mean hs-CRP levels of both treatment groups are shown in Figure 3 and Table 2. In the group 1, at the end of first month there was a 21% decrease in hs-CRP levels compared to the basal measurements (p=0.04). There was no further decrease at the end of three months with the levels achieved at the end of first month were well preserved. In the group 2, the decrease in hs-CRP levels at the end of one month was more striking (37%, p=0.03). However, there was again no statistically significant difference in the effects of both treatment arms on hs-CRP levels, (p=0.08) (Fig. 4, Table 2).

Both types of treatment were well tolerated by the patients. None of the patients had increased blood transaminases and creatinine kinase levels during the study. None of the patients stopped using the medication due to any adverse effects or intolerance.

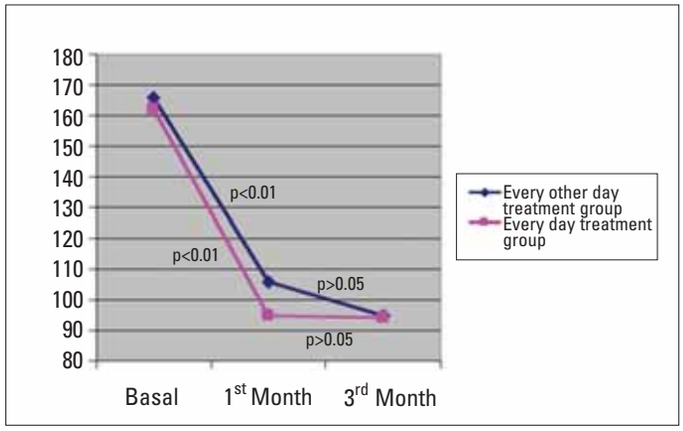

Figure 1. The changes in mean LDL-cholesterol levels (mg/dl) in both groups
LDL - low-density lipoprotein

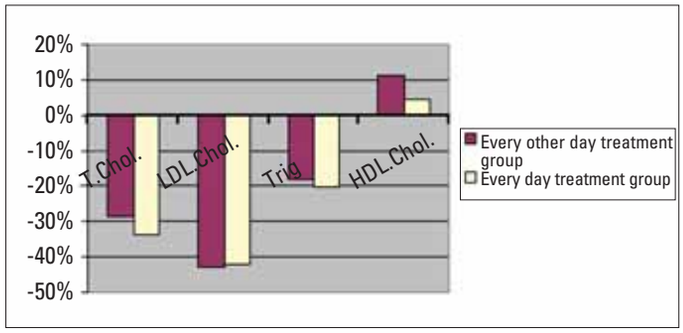

Figure 2. The changes in lipid parameters at the end of third month in both groups (p>0.05 for all parameters between two groups)
HDL. Chol. –high-density lipoprotein cholesterol, LDL.Chol. – low-density lipoprotein cholesterol, T.Chol. – total cholesterol, Trig. - triglycerides

Table 2. Lipid parameters and hs-CRP (mean±SD) of the groups

Variables	Basal	1st month	3rd month	F•	p•
Total cholesterol, mg/dl					
Group 1	244±26	176±26*	175±29*‡	65.9	<0.01
Group 2	242±29	165±31*	161±33*‡	67.5	<0.01
2 way interaction					NS
LDL cholesterol, mg/dl					
Group 1	166±25	106±25*	95±31*‡	60.8	<0.01
Group 2	162±23	95±24*	94±28*‡	78.8	<0.01
2 way interaction					NS
HDL cholesterol, mg/dl					
Group 1	45±7	42±7†	50±19*¥	3.5	0.04
Group 2	47±12	45±11†	49±14†‡	1.1	NS
2 way interaction					NS
Triglycerides, mg/dl					
Group 1	163±64	136±41†	137±57†‡	2.27	NS
Group 2	159±55	117±41*	127±51†‡	5.3	0.04
2 way interaction					NS
Hs-CRP, mg/dl					
Group 1	4.3±5.6	3.4±3.9*	3.2±3.5*‡	1.9	0.04
Group 2	6.9±5.8	4.3±3.6*	4.4±4.3*‡	2.8	0.03
2 way interaction					NS

Two-way ANOVA for repeated measurements
• - F and p values for intragroup comparison of variables
*: <0.05 compared to the basal levels, †: >0.05 compared to the basal levels, ‡: >0.05 compared to the levels at the first month, ¥ : <0.05 compared to levels at the first month - posthoc Tukey test for comparison of variables between groups
Group 1 - treatment every other day
Group 2 - treatment every day
HDL - high-density lipoprotein, Hs-CRP - high sensitive C-reactive protein, LDL - low-density lipoprotein

Discussion

In our study, alternate-day dosing of atorvastatin caused a significant lipid-lowering and antiinflammatory effects similar to that of daily administration. In large-scale randomized studies carried out with statins (1-3), significant effects were shown in coronary artery disease risk, and their use in primary and secondary prevention increased significantly. This resulted in an increase in health expenses. Atorvastatin has been shown to reduce LDL levels up to 60% in a dose-dependent manner (12). Although being so powerful antihyperlipidemic drug, it is also quite expensive, costing up to $700 for a one-year tablet supply in retail pharmacies (13). A cost analysis of alternate-day treatment with atorvastatin has demonstrated a reduction in expenditure based on 1% LDL reduction per patient (6). Because of the long-lasting active metabolites of atorvastatin, the half-life of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition reaches 20-30 hours (12, 14). Conceivably, alternate-day treatment with atorvastatin might be effective in maintaining the lipid-lowering efficacy. Therefore, the use of alternate-day dosing could result in annual cost savings and better compliance without any decrease in lipid-lowering efficacy (15, 16).

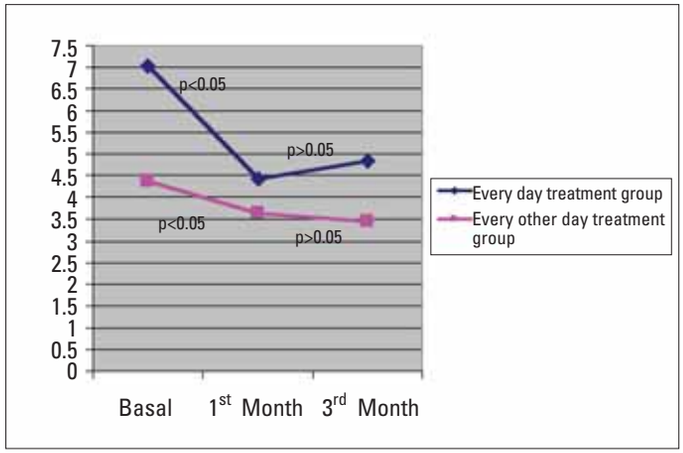

Figure 3. The changes in mean hs-CRP (mg/L) levels in both groups
Hs-CRP – high sensitive C-reactive protein

Previous studies show that alternate-day atorvastatin is an efficacious and safe alternative to daily dosing in lowering blood cholesterol levels (6, 7, 9, 15). Recently, Mackie BD et al. reported that alternate-day regimen of rosuvastatin, which has a

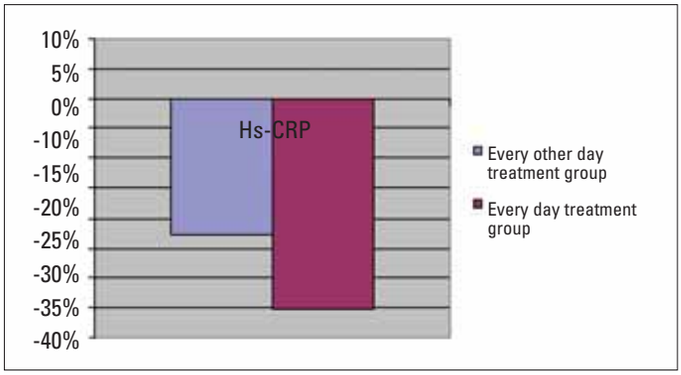

Figure 4. Comparison of hs-CRP levels changes at the end of third month in both groups (p>0.05)
Hs-CRP - high sensitive C-reactive protein

long half-life and very potent statin like atorvastatin, is very efficacious in lowering LDL-cholesterol levels and well-tolerated even in patients previously intolerant to statin therapy (17). In our study, the group that received atorvastatin every other day had 28.3% decrease in total cholesterol levels, 42.7% decrease in LDL cholesterol levels, 18.1% decrease in triglyceride levels and 11.1% increase in HDL cholesterol levels at the end of three months of treatment. Although the decrease in LDL-cholesterol levels was faster (mean LDL-cholesterol<100 mg/dl at the end of the first month) in the standard treatment group (20 mg atorvastatin daily), both groups had mean LDL levels of lesser than 100 mg/dl at the end of three months. Thus, similar to previous reports (6, 7, 9, 15), in our study, alternate-day dosing of 20 mg atorvastatin resulted in a similar reduction in the total and LDL-cholesterol levels compared to daily dosing with a similar tolerance.

Although it is thought that the real clinical benefits of statins are due to their LDL lowering effects, the benefit observed in clinical trials is beyond that of lowering LDL; the fact that such an effect was observed before lipid lowering effect resulted in their anti-inflammatory properties being popularized (18). Since statins have been reported to have strong associations with hs-CRP reduction and prevention of coronary events (19-22) atorvastatin could expert its anti-atherosclerotic effects through a mechanism involving reduction of hs-CRP (23). Similarly, Ridker et al. reported that aggressive use of statin therapy, to achieve target levels of both LDL cholesterol and CRP, decreases the risk of recurrent myocardial infarction and death among patients with acute coronary syndromes (24). Nissen et al. reported that magnitude of change in LDL cholesterol levels and magnitude of change in CRP levels were both independent predictors of plaque regression after statin therapy (25, 26). In our study, there was a significant decrease in the levels of hs-CRP in both groups (22.7% p=0.04 vs 35.1% p=0.03 after 3 months of treatment). The group receiving the pill every day had more significant decrease in hs-CRP levels, however the difference between the two groups did not reach the level of statistical significance. The decrease was observed at the end of the first month in both groups and there was no additional change at the end of third month. Thus, we demonstrated that the alternate-day administration of atorvastatin can produce a reduction in not only LDL-cholesterol but also hs-CRP levels comparable to that of daily administration in patients with hypercholesterolemia.

Study limitations

Our study has several limitations. First, this study included only a limited number of patients from a single center. We have no data about clinical end-points because of short term follow-up period.

Conclusion

Atorvastatin 20 mg daily and every other day resulted in a similar decrease in LDL cholesterol and hs-CRP levels. Our results suggest that alternate-day dosing of atorvastatin may be an effective alternative to daily dosing in lipid lowering; therapeutic outcome is not diminished. Furthermore, alternate-day therapy results in a similar reduction in hs-CRP levels comparable to that of daily administration suggesting the maintenance of anti-atherosclerotic effects of statins. In conclusion, alternate-day dosing of atorvastatin causes significant lipid–lowering and antiinflammatory effects similar to that of daily administration and yet provide some cost savings.

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