

Comparison of Three Different Cholesterol Lowering Treatment Modalities on Markers of Inflammation

Farklı Üç Kolesterol Düşürücü Tedavi Yönteminin İnflamatuar Markerler Üzerine Etkisi

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ABSTRACT Objectives: This study compares the efficacy of three different cholesterol-lowering treatment modalities (10/10 mg of ezetimibe plus simvastatin, 40 mg of atorvastatin and 10/10 mg of ezetimibe plus atorvastatin) on several biochemical markers of inflammation and carotid artery intima-media thickness. **Material and Methods:** One hundred four consecutive patients (69 male and 35 female, with a mean age of 53 ± 8 years) with hyperlipidemia, who were in need of high doses of lipid lowering therapy, were included in the study. The patients were prospectively randomized to three different modalities. After 6 months of therapy initial examinations of lipid indices, several biochemical markers of inflammation and carotid artery intima-media thickness measurements were rechecked. Efficacy of these regimens on lipid indices and inflammatory markers were compared. **Results:** All the regimens showed a significant decrease in LDL and they showed a decline in levels of inflammatory markers except SAA. In 10/10 mg of ezetimibe plus simvastatin group the reduction of tumor necrosis factor alpha and in all groups the reduction of high sensitive C-reactive protein reached significance. Also right carotid intima media thickness decreased significantly in atorvastatin group. **Conclusion:** All three regimens can be preferred for patients who need high doses of lipid lowering therapy. When lipid goals were concerned, three regimens were equal. Furthermore, beneficial effects on markers of inflammation were also similar.

Key Words: Hydroxymethylglutaryl-CoA reductase inhibitors; atherosclerosis

ÖZET Amaç: Bu çalışmada farklı üç kolesterol düşürücü tedavi yönteminin (10/10 mg ezetimib + simvastatin, 40 mg atorvastatin, 10/10 mg ezetimib + atorvastatin) inflammatuar biyomarkerler ve karotis intima media kalınlığı üzerine olan etkisini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Çalışmaya yüksek dozlarda lipid düşürücü tedaviye ihtiyaç duyan ardışık 104 (65 erkek, 35 kadın, ortalama yaşları 53 ± 8) hasta alındı. Hastalar prospektif olarak üç farklı tedavi yöntemine randomize edildiler. İlk başvurularında ve tedavinin altıncı ayında karotis intima media kalınlığı, inflammatuar markerler açısından kontrol edildi. Tedavi rejimlerinin lipid profili ve inflammatuar markerler üzerine olan etkisi değerlendirildi. **Bulgular:** Her üç tedavi rejimi de belirgin LDL düşüşü ve serum amiloid A dışındaki inflammatuar markerlerde azalma sağladı. Diğer gruplara göre tümör nekroz faktör alfa 10/10 mg ezetimib + simvastatin alan grupta, yüksek duyarlılıklı CRP ise bütün gruplarda anlamlı düşüş gösterdi. Ayrıca atorvastatin grubunda sağ karotis intima media kalınlığı anlamlı olarak azaldı. **Sonuç:** Her üç tedavi rejimi de yüksek dozda lipid düşürücü tedaviye ihtiyaç duyulan hastalarda tercih edilebilir. Lipid tedavi hedeflerine ulaşma açısından her üç tedavi yöntemi eşit bulundu. İnflamatuar markerler üzerindeki yararlı etkileri de benzerdi.

Anahtar Kelimeler: HMG Co A inhibitörleri; ateroskleroz

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Statins have been shown to reduce coronary mortality in both primary and secondary prevention trials. Anti-inflammatory effects of statins have also been well documented. Since atherosclerosis is recognized as

an inflammatory disease, clinical improvement with statin therapy may in part be attributed to the effect of statins on the systemic anti-inflammatory profile. The effects of pravastatin, simvastatin, lovastatin and atorvastatin on these parameters have been shown in previous studies.¹⁻⁴ Ezetimibe is a new lipid-altering agent that inhibits the absorption of cholesterol at the intestinal brush border.⁵ Combination of ezetimibe with atorvastatin or simvastatin was proved to be well tolerated and more efficacious than monotherapy.⁶⁻⁸ Furthermore several recent studies showed that ezetimibe co-administered with simvastatin or atorvastatin resulted in significant decreases in high sensitive C-reactive protein (hsCRP), possibly consistent with an additional anti-inflammatory effect compared with simvastatin monotherapy.⁹⁻¹¹ We compared three different treatment modalities, being 10/10 mg of ezetimibe plus simvastatin, 40 mg of atorvastatin and 10/10 mg of ezetimibe plus atorvastatin on lipid indices and on various markers of inflammation including hsCRP, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), serum amyloid A (SAA), homocysteine and carotid artery intima-media thickness (IMT).

MATERIAL AND METHODS

PATIENTS

The current open label randomized study was carried out in the Department of Cardiology, Duzce University Faculty of Medicine, between February 2005 and 2007. One hundred four consecutive patients with hyperlipidemia (69 male and 35 female, with a mean age of 53 ± 8 years) were included in the study. Patients with a lipid profile that need high doses of cholesterol lowering therapy; strictly speaking a reduction of > 40% of low-density lipoprotein (LDL) cholesterol, were considered for enrollment. Target lipid goals were defined according to the modified ATP III criteria.¹² Patients with acute coronary syndromes, stroke, coronary angioplasty or major surgery during the last three months, acute state of a chronic infectious or inflammatory disease, anticoagulant therapy, severe liver or renal disease, neoplasm and hematological disorders were excluded. Every patient signed an

informed consent. Local ethics committee has approved the study (2005/06-1).

All of the patients were underwent a comprehensive physical examination. Medical histories and personal characteristics were recorded. After baseline blood samples were drawn, the patients were randomized either to 10 mg simvastatin plus 10 mg ezetimibe combination (ES), 40 mg atorvastatin (maximum commercial dose available in our country at the time of the study) or 10 mg atorvastatin plus 10 mg ezetimibe combination (EA) daily. All the patients were re-evaluated after six months of therapy for comparison.

BLOOD SAMPLING AND BIOCHEMICAL ANALYSIS

Serum samples were analyzed in the Department of Biochemistry, Duzce University Faculty of Medicine. Blood samples were collected after 12 hours of fasting from the antecubital vein under standardized conditions for determination of routine biochemical analysis including glucose, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, triglyceride, hsCRP, IL-6, TNF, SAA and homocysteine. Serum and plasma samples were separated immediately after collection and centrifuged at 3,000 g for 15 min. All samples were kept frozen at -20°C for analysis of inflammatory markers. All laboratory determinations were performed in duplicate and in a blinded manner.

Serum levels of total cholesterol, HDL and triglyceride were measured in an automated analyzer (Olympus AU640, Hamburg, Germany) using commercially available kits (Olympus Diagnostica GmbH, Hamburg, Germany). LDL cholesterol was measured according to Friedewald's formula. hsCRP, IL-6, TNF- α measurements were obtained by chemiluminescent enzyme immunoassay method with use of commercially available kits (DPC, USA) and automatic hormone analyzer (Immulite, BioDPC, USA). The detection limit and reference range for the hsCRP assay were 0.1 mg/L and 1.4-11 mg/L, respectively. The reference ranges were 0-3.4 $\mu\text{g/L}$ for IL-6 and 0-8.1 $\mu\text{g/L}$ for TNF- α . SAA concentrations were measured in duplicate, by ELISA kit (BioSource International, Camarillo, Ca-

lif USA). Analysis of plasma homocysteine was performed using high-performance liquid chromatography with fluorescence detection (reference range 0-18 $\mu\text{mol/L}$).

CAROTID ARTERY INTIMA-MEDIA THICKNESS MEASUREMENT

The right and left carotid arteries were examined with a duplex scanner (Hitachi EU 5600, Hitachi Medical Corporation, Japan) by using a 7.5 MHz linear array transducer. The patients were investigated in the supine position with the head slightly turned from the sonographer. The same trained sonographer performed all scans. The carotid arteries were carefully examined with regard to wall changes. The far wall of the common carotid artery (CCA), 0.5-1.0 cm proximal to the beginning of the carotid bulb, was used for measurements of the intima-media thickness (IMT). The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo.

STATISTICAL ANALYSIS

Values are presented as mean \pm standard deviation. Categorical data were compared with χ^2 test. All the basic numeric data were checked for normal distribution. Parametric statistics were used calculating mean values and standard deviations. Normally distributed data were evaluated using one-way ANOVA, followed by a post hoc Scheffe's

test. Paired t-test was used to compare the data before and after therapy for the same group of patients. For skewed distribution data analysis was carried out by the Kruskal-Wallis test, followed by post hoc Bonferroni adjustment. The Wilcoxon Rank Sum Test carried out for "in-group" analysis. Statistical analyses were carried out using the SPSS 10.0 for Windows. A p value of < 0.05 was considered significant.

RESULTS

The baseline characteristics of the study population are given in Table 1. Age, body mass index (BMI), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), HDL, hsCRP and TNF- α were not distributed normally among the groups. Three groups had similar characteristics. Although they were in the normal regimen, SGOT and SGPT levels were significantly different among the groups. However, the safety profile of both atorvastatin and combination therapies was good and no patient had any side effects leading to the discontinuation of therapy.

At the end of the treatment all the regimens showed a significant ($p < 0.001$ for all groups) decrease in the mean levels of total serum cholesterol and LDL (Table 2). Percent change in LDL was 37%, 41% and 44% in ES, atorvastatin and EA groups, respectively. There was also a statistically sig-

TABLE 1: Baseline characteristics of the study groups

Variable	ES (n= 35)	Atorvastatin (n= 35)	AE (n= 34)	p value
Age (mean \pm SD)	53 \pm 7	53 \pm 8	54 \pm 7	0,228
Sex (female; n) (%)	12 (34%)	8 (23%)	15 (43%)	0,103
BMI (mean \pm SD)	32 \pm 2	31 \pm 2	33 \pm 2	0,166
Smokers; (n) (%)	12 (34%)	13 (37%)	7 (20%)	0,298
Hypertension; (n) (%)	24 (68%)	25 (71%)	17(49%)	0,147
Diabetes; (n) (%)	9 (26%)	11 (31%)	14 (40%)	0,296
SGOT (mg/dL) (mean \pm SD)	21 \pm 10 [#]	21 \pm 9*	25 \pm 10	0,001
SGPT (mg/dL) (mean \pm SD)	20 \pm 7 [§]	24 \pm 10	25 \pm 8	0,035

#ES vs. AE; p: 0.002.

§ES vs AE; p: 0.013.

*Atorvastatin vs AE; p: 0.001.

(ES: 10 mg ezetimibe plus 10 mg simvastatin combination, EA: 10 mg ezetimibe plus 10 mg atorvastatin combination, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvate transaminase, BMI: body mass index, CAD: coronary artery disease, CCB: calcium channel blocker).

TABLE 2: Comparison of the treatment groups on lipid indices

	Variable	Baseline (mean \pm SD)	After treatment (mean \pm SD)	p value
ES (n= 35)	Total cholesterol (mg/dL)	256 \pm 27	192 \pm 40	< 0.001
	HDL (mg/dL)	51 \pm 11	50 \pm 11	0.143
	LDL (mg/dL)	170 \pm 23	107 \pm 27	<0.001
	Triglyceride (mg/dL)	179 \pm 82	184 \pm 88	0.687
Atorvastatin (n= 35)	Total cholesterol (mg/dL)	262 \pm 29	182 \pm 33	< 0.001
	HDL (mg/dL)	49 \pm 9	50 \pm 9	<0.001
	LDL (mg/dL)	173 \pm 19	101 \pm 29	<0.001
	Triglyceride (mg/dL)	187 \pm 65	165 \pm 74	0.11
EA (n= 34)	Total cholesterol (mg/dL)	278 \pm 35	184 \pm 39	< 0.001
	HDL (mg/dL)	50 \pm 7	49 \pm 8	0.001
	LDL (mg/dL)	189 \pm 31	104 \pm 30	<0.001
	Triglyceride (mg/dL)	213 \pm 88	184 \pm 93	0.03

(ES: 10 mg ezetimibe plus 10 mg simvastatin combination, AE: 10 mg ezetimibe plus 10 mg atorvastatin combination, HDL: high density lipoprotein, LDL: low density lipoprotein)

nificant decrease in triglyceride levels after treatment with EA. The change in HDL levels was significantly different in atorvastatin and EA groups possibly because of abnormal distribution. The mean resulting change was relatively small (< 2%).

At the end of the treatment 40 mg daily atorvastatin showed a significant decrease in right carotid artery IMT (Table 3).

All the regimens showed a decline in levels of inflammatory markers except SAA. The reduction of TNF- α in 10/10 mg of ezetimibe plus simvastatin group and hsCRP in all groups reached significance (Table 3).

DISCUSSION

The present study showed that 40 mg atorvastatin, 10/10 mg ES or 10/10 mg EA combinations are equally effective treatment modalities when aggressive lipid lowering therapy needed. Furthermore, they had anti-inflammatory effects beyond their lipid lowering effects. However, we admit that this is a relatively small-scale study and larger scale studies should be conducted in order to increase the power of statistical analysis. Neither regimen significantly lowered SAA levels in our study group.

More than 20 prospective epidemiologic studies demonstrate that hsCRP is an independent

predictor of risk of myocardial infarction and sudden cardiac death even in apparently healthy individuals.¹³ SSA and IL-6 have also been shown to be associated with increased risk of future cardiovascular events.^{14,15} Plasma levels of TNF- α are persistently elevated among patients at increased risk for recurrent coronary events.¹⁶ Homocysteine, on the other hand, has been established as an independent risk marker for atherosclerosis.¹⁷ Elevation of these markers reflects the low degree of inflammatory response due to the local inflammation in atherosclerotic tissue. Carotid IMT, on the other hand, is a simple and inexpensive tool to assess the cumulative effect of atherosclerotic risk factors and is established as an independent predictor of future cardiovascular risk.¹⁸

Statins show their anti-inflammatory effects by lowering the plasma levels of these acute phase reactants beyond their lipid lowering effects. Wiklund et al. compared simvastatin and atorvastatin in means of inflammatory marker lowering effects and found that hsCRP and SAA levels were reduced only by atorvastatin.¹⁹ For ICAM-1 and IL-6 they found only a very small reduction, similar for both compounds. Our results are in parallel with this study except that we could not confirm any reduction in SAA levels.

TABLE 3: Comparison of the treatment groups on markers of inflammation

	Variable	Baseline (Mean ± SD)	After treatment (Mean ± SD)	p value
ES (n= 35)	Homocysteine (µmol/L)	24 ± 11	19 ± 18	0.322
	hsCRP (mg/L)	1.18 ± 1.63	0.65 ± 0.94	<0.001
	SAA (mg/L)	4.1 ± 2.1	5.7 ± 2.1	0.165
	IL-6 (µg/ L)	6.6 ± 0.8	6.7 ± 0.3	0.775
	TNF-α (µg/ L)	11 ± 3.7	7.4 ± 2.2	0.021
	Right CIMT (cm)	0.70 ± 0.14	0.66 ± 0.12	0.234
	Left CIMT (cm)	0.72 ± 0.16	0.69 ± 0.11	0.165
Atorvastatin (n= 35)	Homocysteine (µmol/L)	20 ± 12	18 ± 8	0.28
	hsCRP (mg/L)	1.15 ± 1.11	0.59 ± 0.61	0.015
	SAA (mg/L)	5.2 ± 2.7	4.6 ± 2.3	0.562
	IL-6 (µg/ L)	6.1 ± 1.3	5.6 ± 2.3	0.205
	TNF-α (µg/ L)	9 ± 4.6	6.9 ± 1.6	0.154
	Right CIMT (cm)	0.67 ± 0.10	0.65 ± 0.11	0.035
	Left CIMT (cm)	0.71 ± 0.11	0.70 ± 0.15	0.233
AE (n= 34)	Homocysteine (µmol/L)	14 ± 6	11 ± 7	0.454
	hsCRP (mg/L)	1.04 ± 1.78	0.44 ± 0.48	0.006
	SAA (mg/L)	4.3 ± 3.1	4.9 ± 2.2	0.572
	IL-6 (µg/ L)	6.9 ± 0.3	6.6 ± 0.5	0.172
	TNF-α (µg/ L)	13.5 ± 3.4	10.6 ± 6.8	0.068
	Right CIMT (cm)	0.65 ± 0.10	0.62 ± 0.09	0.244
	Left CIMT (cm)	0.70 ± 0.11	0.66 ± 0.07	0.168

(ES: 10 mg ezetimibe plus 10 mg simvastatin combination, EA: 10 mg ezetimibe plus 10 mg atorvastatin combination, IL-6: interleukin 6, SAA: serum amyloid A, TNF: tumor necrosis factor, hsCRP: high-sensitivity C-reactive protein; CIMT: carotid intima media thickness)

In our study, hsCRP-lowering effect of all groups reached significance. However, there was a 58% decrease in the mean hsCRP levels (20% more than the atorvastatin monotherapy) after six months of EA therapy suggesting that ezetimibe could potentiate the hsCRP lowering effect of atorvastatin. This result was confirmed by a recent report by Ballantyne et al. who showed that ezetimibe plus atorvastatin resulted in overall 10% median reduction in hsCRP level.⁹ The authors speculated that the mechanism of hsCRP lowering might be associated with an action of ezetimibe to potentiate the hsCRP lowering effect of statins since several other studies reported similar efficacy.^{10,11} The reduction in hsCRP levels increases with the increase in statin dose. It was reported that the reduction in hsCRP was related with a benefit on mortality rate.²⁰ In our study, there was a 45% decrease in hsCRP levels after ES therapy suggesting that ezetimibe could potentiate the hsCRP lowering effect of simvastatin. This result was confirmed by a study conducted by Sager et

al. who showed that ezetimibe plus simvastatin 10 mg/day resulted in a similar degree of hsCRP reduction as simvastatin 80-mg/day monotherapy.¹⁰ Compared with placebo, the reduction in hsCRP by ezetimibe monotherapy was not statistically significant. Conforming our results; Ballantyne et al also reported a 28.6% decrease in mean hsCRP level by atorvastatin 40 mg and 21.1% by ES 10/10 mg combination.²¹ The benefit of ezetimibe to potentiate the hsCRP lowering when added to statins can be used in special patient population who could not tolerate higher doses of statins.

Several studies have shown a reduction of TNF-α by pravastatin and simvastatin.^{22,23} similarly, we showed a significant reduction in TNF-α levels with ES therapy.

Regression of carotid IMT by statin therapy was demonstrated in patients with familial hypercholesterolemia.²⁴ The findings of METEOR study demonstrated that in middle-aged adults with Fra-

mingham risk scores lower than 10% and evidence of subclinical atherosclerosis, 40 mg rosuvastatin treatment resulted in statistically significant reductions in the rate of progression of maximum carotid IMT during a 2 year period compared with placebo.²⁵ A recent study conducted by Yu et al. compared the efficacy of a high dose (80 mg daily) with a low dose (10 mg daily) of atorvastatin regimen on carotid IMT, given for 26 weeks in coronary artery patients. Carotid IMT was reduced significantly in the high-dose group, but was unchanged in the low-dose group at the end of the study.²⁶ In our study all the three regimens showed a tendency for regression in carotid IMT, but only

atorvastatin group could reach statistical significance possibly due to smaller cohort and shorter duration of study.

LIMITATIONS OF THE STUDY

The study cohort is relatively small and the period of re-evaluation is especially insufficient for measuring a significant change in carotid IMT.

CONCLUSION

Either 40 mg of atorvastatin or 10/10 combinations of ES or EA can be preferred for patients requiring intensive lipid lowering and all the three regimens have beneficial effects on inflammation.

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