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# Higher Efficacy of 10 mg/day of Simvastatin in Turkish Patients with Hyperlipidemia

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***HİPERLİPİDEMİLİ TÜRK HASTALARIN GÜNDE 10 mg SİMVASTATİN'E YÜKSEK DUYARLILIĞI***

***ÖZET***

*Hiperlipidemili Türk erişkinlerinin düşük doz simvastatin'e batılı hastalardan daha fazla duyarlı olup olmadığını araştırmak amacıyla çok merkezli bir çalışma yapıldı. 52'si kadın olmak üzere, toplam 86 kişi çalışmaya alınma kriterlerine uydukları görülerek incelemeye dahil edildi (54 ± 9 yaş). Hedef nokta olarak LDL-K düzeyindeki düşme göz önünde tutuldu. Günde 10 mg'lık simvastatin dozu uygulanmak suretiyle başlangıçta erkek ve kadınlarda yüksek olan total kolesterol (256 ve 296 mg/dl), trigliserit (184 ve 177 mg/dl), LDL-kolesterol (177 ve 214 mg/dl), HDL-kolesterol (41 ve 48 mg/dl) üzerine etkiler izlendi. Altı hafta sonunda LDL-K ortalama %31,3, TK %23, TG % 4,5 oranında düştü. HDL-K %5 oranında yükseldi. TK/HDL-K oranı 6,2'den 4,7'ye indi. Bu arada beden kitle indeksinde 28,6'dan 0,5 kg/m²'lik anlamlı bir azalma eşlik etti. Koroner kalp hastalığının varlığı veya sigara içme durumu LDL kolesterol düzeylerindeki değişiklik üzerine etkili görülmedi. İlaca bağlı yan etkiler hastaların 8'inde hafif ila orta derecede gözlemlendi. Türk erişkinlerinde 10 mg simvastatin ile sağlanan LDL-K cevabının, 4S çalışmasında yaklaşık 17 mg simvastatin dozu ile elde edilen LDL kolesterol düşüklüğüne karşılık geldiği hesaplandı.*

*Sonuç olarak, Türk hastaların simvastatin'e batılı populasyonlara kıyasla daha duyarlı olduğu ve ilacın aynı güvenlikte görüldüğü kanısına varıldı.*

***Anahtar kelimeler:*** *Hiperlipidemi, lipoproteinler, statinler, Türk hastalar.*

## INTRODUCTION

Simvastatin is a potent inhibitor of HMG-CoA reductase, the enzyme catalyzing the conversion of hydroxymethylglutarate to mevalonate, an early and rate-limiting step in the synthesis of cholesterol. Simvastatin is an inactive lactone, which is extensively metabolized in the liver to active and inactive compounds following oral administration. The drug is well absorbed (~85% in animal models) and its absorption is not affected by food [1].

In clinical studies, simvastatin was highly effective in reducing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C) concentrations [2]. In addition, simvastatin moderately reduced triglycerides (TGs) and produced variable increases in high-density lipoprotein cholesterol (HDL-C). The recommended dosage range of simvastatin is 5 to 40 mg q.d. At doses of 5, 10, 20, and 40 mg/day, simvastatin reduced LDL-C by 24, 30, 35, and 40%, respectively [3].

Though the clinical efficacy of simvastatin has been well established by the Scandinavian Simvastatin Survival Study [4S] [4], ethnic differences may affect the medication's safety, efficacy, dosage, and dose regimen in different populations. Though all are of Caucasian origin, ethnic differences exist between Western European and Turkish populations. In this study, we hypothesized primarily the LDL-C lowering effect of simvastatin is at least as much in Turkish patients as in previous study populations and secondarily assumed the effects of simvastatin on fasting serum TC, HDL-C and TG levels are as good in Turkish patients with a similar safety profile as in previous study populations.

## MATERIAL and METHODS

### Study Group

Successive patients who fulfilled the following criteria were enrolled: patients between 20-70 years of age and having serum TG levels lower than 400 mg/dL and serum LDL-C >190 mg/dL with with 1 or no risk factor and no coronary heart disease/peripheral vascular disease (CHD/PVD), or serum LDL-C >160 mg/dL with 2 or more risk factors levels and no CHD/PVD, or serum LDL-C >130 mg/dL with clinically evident CHD or PVD according to the NCEP criteria. Patients were requested to fast

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for at least 12 hours prior to each visit and to have signed the informed consent form.

Patients having any of the following criteria were excluded from the trial: serum TG level higher than 400 mg/dL, women who were breast-feeding, pregnant or who planned to become pregnant during the course of the study, patients with uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg), diabetes mellitus or HbA1c levels higher than 10% (though not previously diagnosed as diabetes mellitus), active liver disease or hepatic dysfunction, AST or ALT higher than twice the upper limit of normal range, renal dysfunction (serum creatinine >2.0 mg/dL), types I, III, IV, or V hyperlipidemias, or homozygous familial hypercholesterolemia, nephrotic syndrome, hypothyroidism or any type of myopathy, patients having a myocardial infarction, coronary angioplasty, coronary artery bypass graft surgery within the previous 3 months, severe or unstable angina pectoris within the previous month, alcohol consumption greater than 10 drinks per week, partial ileal bypass or hypersensitivity to HMG-CoA reductase inhibitors, poor mental function or those who had participated in another clinical trial and/or had been administered a study drug, whether an active compound or placebo, within the previous month.

### Study Design

The study was designed to be an open label single-arm multicenter phase IV study. The eligible patients who agreed to participate in the study and signed the informed consents were called for a 6-week treatment period, during which they were requested to take a 10-mg tablet of simvastatin once-a-day.

### Time Schedule of the Study

All patients meeting the LDL-C level criteria were screened for the entry criteria and the eligible ones were called for Visit 1. At Visit 1, patients have come to the clinic fasted for at least 12 hours. Medical history, body weight, vital signs were taken and blood samples were drawn for lipid and other laboratory measurements. Patients were instructed to consume a standard diet throughout the study period in order not to cause a weight increase during the study. At Visit 2, patients were given two blisters each including 14 tablets (total 28 tablets) of 10 mg simvastatin. Each patient was requested to take one tablet at bedtime and a missed dose was allowed to be taken up to six hours later than the scheduled time but no later.

At Visit 3 performed on day 21, the patient's vital signs and compliance to diet and drug were assessed. The assessment of lipid analysis was also performed. Blisters were collected from the previous 3 week period and tablets were counted. Compliance was determined by the following formula: 28 minus number of returned tablets/number of days between visits X 100. Those whose drug compliance was <60% were subsequently excluded from the study. Thereafter, patients were given two new blisters each including 14 tablets (total 28 tablets) of 10 mg simvastatin and required to return all unused drugs to the physician at Visit 4. At Visit 4, on day 42, a full physical examination was carried out, compliance to diet and drug was assessed and blood samples were drawn for lipid analysis and other laboratory measurements. Compliance assessment was repeated as described above. Adverse experience monitoring was also performed.

### Prior and Concomitant Medication(s)/Treatment(s)

The usage of lipid lowering agents, including bile acid sequestering resins, HMG-CoA reductase inhibitors, nicotinic acid, fibrates and derivatives, taken within 3 months and probucol taken within 1 year prior to Visit 1 was not allowed. The usage of the following drugs was not allowed: immunosuppressive drugs or systemic antifungal agents of the azole class, including itraconazole and drugs that are known to increase the risk of rhabdomyolysis, systemic steroids within the previous 3 months and chronic systemic glucocorticoid therapy, isotretinoin (e.g. accutane), regular usage of antacids, anticoagulants, beta-blockers, over the counter fish-oil or niacin in doses >200 mg/day, estrogen replacement therapy in women within the previous 3 months, oral contraceptives, insulin, and thyroxine within the previous 3 months. Patients receiving regular, maintenance doses of metamucil (psyllium) were enrolled provided they have been on a stable dose for at least 1 month and the dose was expected to remain stable during the trial.

### Efficacy and Safety Measurements

The efficacy measurements consisted of assessment of serum levels of TC, HDL-C, TG and LDL-C. The main efficacy parameter, the percent change in LDL-C, was calculated according to the following formula: $LDL\text{-}C_{Visit\ 1}$-$LDL\text{-}C_{Visit\ 4}/LDL\text{-}C_{Visit\ 1}X100$. The laboratory safety measurements performed by a central laboratory were as follows: HbA1c at Visit 1 and BUN, creatinin, AST, ALT, AP, uric acid, CK and complete blood count at Visits 1 and 4. At the end of the sixth week (Visit 4, Last Visit), the efficacy and the safety of simvastatin and also patient compliance were evaluated.

### Statistical Analysis

Since the study sought for a different response pattern to a drug in an ethnic population, the power of the study was set as high as 95%. In order to assess a clinically significant difference of 5% from 35% in primary efficacy parameter (percent decrease in serum LDL-C level) with a standard deviation of 12% at an $\alpha$-error of 0.05, $\beta$-error of 0.05 and a dropout rate of 20%, the calculated sample size was about 100 patients (actual sample size is 97 patients).

The results were expressed as mean, standard deviation, range and %95 confidence interval for normally-distributed data; median, range, interquartile range, for non-normally-distributed numeric data or ordinal data and proportion and %95 confidence interval, when possible, for nominal data. Possible effect of baseline serum LDL-C level on treatment effect was checked by the analysis of covariance (ANCOVA), in which "baseline serum LDL-C level" was included as covariate. Also, possible difference in effect of treatment between centers was checked by including the center-by-effect interaction term in this model.

As there was no significant effect of covariate or the cen-

ter-by-effect term, these terms were excluded from the model and the final model was paired samples Student's t test or Wilcoxon signed-rank test, depending on the characteristics of data, for the analysis of the main efficacy parameter of percent difference in serum LDL-C levels between day 0 and day 42. In case of comparison of other two points (e.g. baseline vs day 21), alpha level was downward adjusted by dividing 0.05 to the number of nonorthogonal comparisons in order to avoid significance inflation. For analysis of comparisons between centers, oneway analysis of variance (ANOVA) test was used. In case of significant result after ANOVA, intergroup comparisons were performed by post-hoc Tukey test. Intergroup comparisons between dichotomous variables such as female-male, CHD positive-negative, smoker-nonsmoker were performed by independent samples Student's t test. All significance tests were two-tailed. Statistical significance was assigned to p values less than 0.05 for the primary or secondary parameters of the trial, less than 0.10 for the interaction terms. Alpha level of individual tests was downward adjusted if multiple pairwise comparison was performed. Statistical Package for Social Sciences (SPSS) v.7.5 for Windows was used to analyze the data.

## RESULTS

### Study Group

Between 27 March 1998 and 30 September 1998, a total of 107 patients were recruited in a total of six centers. Among them, 21 patients were ineligible for the study due to following reasons: 5, did not meet NCEP criteria; 4, TG >400 mg/dL; 4, LDL-C <130 mg/dL; 1, HbA1c >%10; 1, high AST/ALT; 1, high creatinine level; 1, high CK level; 1, refusal give informed consent. The distribution of 86 eligible patients according to the participating centers is given in Table 1. The data regarding the demographic features and baseline evaluations are given in Table 2.

**Table 1. Distribution of the eligible patients by gender and the participating centers**

| Center No* | Female n (%) | Male n (%) | Total n |
|---|---|---|---|
| 1 | 9 (47.4) | 10 (52.6) | 19 |
| 2 | 5 (38.5) | 8 (61.5) | 13 |
| 3 | 17 (81.0) | 4 (19.0) | 21 |
| 4 | 6 (54.5) | 5 (45.5) | 11 |
| 5 | - | 4 (100) | 4 |
| 6 | 15 (83.3) | 3 (16.7) | 18 |
| Total | 52 (60.5) | 34 (39.5) | 86 |

* *See acknowledgements for the participating centers.*

**Table 2. Demographic features of the study group (n=86)**

| Demographic features | |
|---|---|
| Age years, mean±SD (range) | 53.8±9.2 (35.0-70.2) |
| Smoking, pack-year, mean±SD (range) | 21.7±9.0 (5.0-40.0) |
| Physical activity, n (%) | |
| Active/Medium/Sedentary | 13 (15.1)/35 (40.7)/38 (44.2) |
| Associated disease, n (%) | |
| Absent/Present | 24 (27.9)/62 (72.1) |
| Concomitant drug usage, n% | |
| Absent/Present | 36 (41.9)/50 (58.1) |
| **Baseline evaluation, mean±SD (range)** | |
| Height, cm | 160.8±8.9 (137-186) |
| Weight, kg | 73.9±12.9 (44-100) |
| Body mass index, kg/m$^2$ | 28.6±4.5 (17.9-40) |
| Pulse rate, min-1 | 79.1±6.0 (62-100) |
| Systolic blood pressure, mmHg | 131.4±16.1 (100-180) |
| Diastolic blood pressure, mmHg | 82.3±7.6 (60-100) |

### Assessment of Study Variables

In order to assess the treatment effect (simvastatin; 10 mg per day), the difference of the efficacy variables of TC, HDL-C, TG and LDL-C at the time of last visit from baseline was calculated as absolute and percent change values. There was a decrement in TC, TG and LDL-C levels, whereas there was increase in HDL levels in both absolute and percent change values (Figures 1-4, Table 3). The most marked difference was in LDL-C levels with a mean decrease of 31.3% from baseline at the time of last visit. Subgroup analysis performed according to sex, presence of CHD and status of smoking revealed statistically similar values for the percent change in LDL-C levels. The initial level of LDL-C, which was significantly higher in females compared to males (p=0.0002, Table 3), was documented to have a statistically significant impact on the absolute changes (p=0.01) but not reflected to percent change values (-33.9% vs -27.3%, p=0.26). Subgroup analysis revealed a trend toward a greater increase in HDL-C levels in response to simvastatin in those subjects with the lowest baseline HDL-C levels (<35 or 40 mg/dl) (Table 4).

The mean levels of the parameters of pulse rate, systolic blood pressure and diastolic blood pressure at the time of last visit were statistically similar to

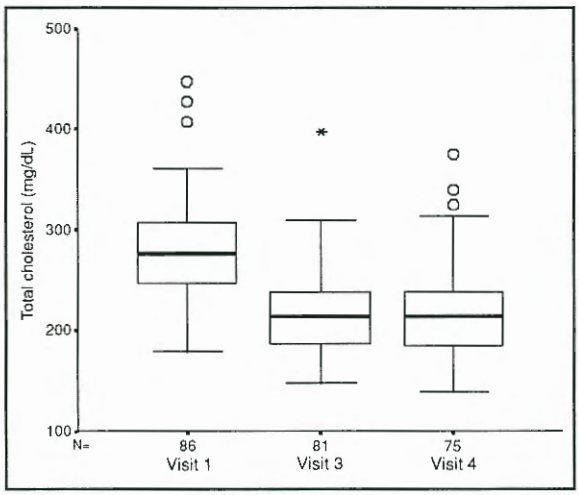


**Figure 1.** Boxplot graph of total cholesterol levels of the study group at the time of follow-up visits.

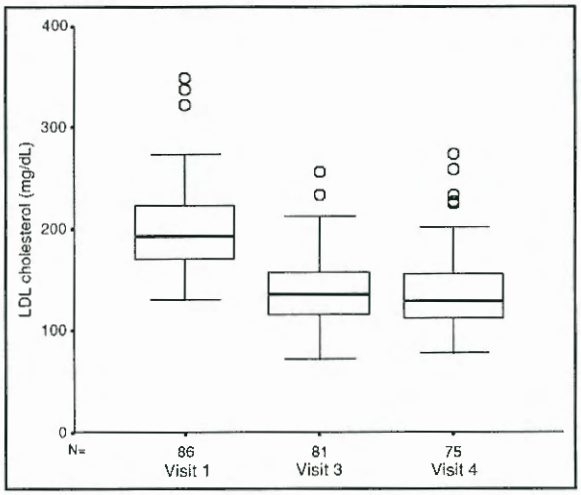


**Figure 3.** Boxplot graph of LDL cholesterol levels of the study group at the time of follow-up visits

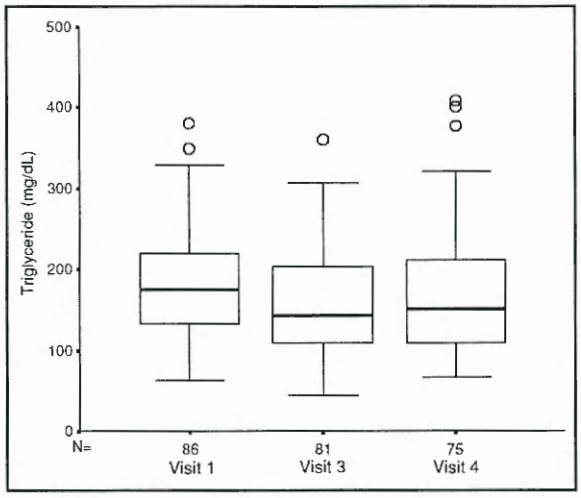


**Figure 2.** Boxplot graph of triglyceride levels of the study group at the time of follow-up visits

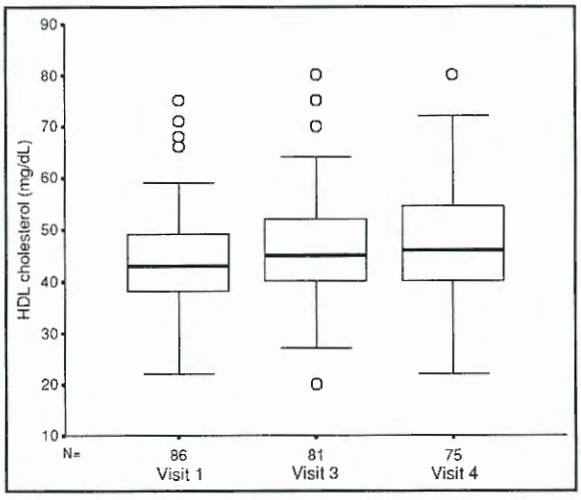


**Figure 4.** Boxplot graph of HDL cholesterol levels of the study group at the time of follow-up visits

baseline. The mean decrease of 0.9±1.8 kg in the body weight of the study group at the time of last visit was statistically significant ($p<0.01$) compared to the baseline level. Likewise, there was a statistically significant ($p=0.00004$) mean decrease of 0.5±0.9 kg/m$^2$ in the BMI of the patients. The mean values of safety laboratory variables of BUN, creatinin, AST, ALT, AP, uric acid, CK and complete blood count were statistically similar ($p>0.05$ for all) at the time of last visit compared to baseline levels.

### Analysis of Compliance

At the time of Visit 3, a total of 5 patients were subsequently excluded from the study. The reasons for exclusion at Visit 3 were lost to follow-up in 3 patients, termination of study in 1 patient and adverse reaction in 1 patient. At the time of Visit 4, 4 more patients were lost to follow-up and 1 patient were subsequently excluded due to the termination of study protocol; thus a total of 76 patients were available for compliance analysis. Throughout the treatment duration, the mean±SD (range) overall compliance rate was 97.3±5.6% (78%-112%).

### Adverse Effects

The adverse effects possibly related to simvastatin at the studied dose consisted of cramp (1 patient), headache (1 patient), myalgia (1 patient), meteorism (1 patient), skin rash (2 patients) and dyspeptic complaints (2 patients). The side effects were usually mild

**Table 3. Effect of simvastatin (10 mg/day for 3 and 6 weeks) on plasma lipids and lipoproteins (mg/dl; mean±S.D.) in Turkish males and females**

| | Triglyceride | Total cholesterol | LDL-C | HDL-C | TC:HDL-C ratio |
|---|---|---|---|---|---|
| **Males** | | | | | |
| Baseline (n=34)[a] | 184±65 | 256±36 | 177±30 | 41±10 | 6.2 |
| 3 weeks (n=32) | 159±54 | 207±39 | 132±34 | 43±9 | 4.8 |
| 6 weeks (n=30) | 173±79 | 204±49 | 128±40 | 42±12 | 4.9 |
| % difference (baseline versus 6 weeks) | ↓3% | ↓21% | ↓28% | ↑3% | |
| **Females** | | | | | |
| Baseline (n=52)[a] | 177±67 | 296±46 | 214±44 | 48±10 | 6.2 |
| 3 weeks (n=49) | 153±68 | 224±41 | 144±33 | 49±10 | 4.6 |
| 6 weeks (n=45) | 164±80 | 226±40 | 142±37 | 51±10 | 4.4 |
| % difference (baseline versus 6 weeks) | ↓6% | ↓24% | ↓37% | ↑7% | |

[a]*n= number of individuals in the group at each time point*

to moderate in intensity except a severe cramp attack in one patient. In 2 patients (one with skin rash and the other with cramp attack) treatment was withdrawn. There were no statistically significant differences in the mean values for the various laboratory parameters during treatment as compared to baseline, and only mild elevations (less than 1.5-fold above normal) were observed. Those individuals with such mild elevations were as follows: serum creatinine (n=5; 5.8% of study group); BUN (n=1, 1.2%); uric acid (n=22, 25.6%), AP (n=17, 19.8%), ALT (n=2, 2.3%) and CK (n=2, 2.3%). Significant changes in liver function tests are typically more than 3 times normal. Furthermore, CK levels are greater than 10-fold higher than normal.

## DISCUSSION

Hyperlipidemia is one of the major risk factors for the development of CHD and progression of atherosclerotic lesions. Dietary therapy together with hypolipidemic drugs are central to the management of hyperlipidemia and aim to prevent atherosclerotic plaque progression, induce regression, improve endothelial dysfunction [5], and thus decrease the risk of acute coronary events in patients with pre-existing coronary or peripheral vascular disease. The HMG-CoA reductase inhibitors, or statins, are the most potent lipid-lowering agents currently available. Six drugs that act as specific inhibitors of HMG-CoA reductase - lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and most recently, cerivastatin - have been approved throughout the world. Comparative studies in patients with primary hypercholesterolemia revealed the log-linear dose response curves for all these drugs but indicate that lovastatin and pravastatin are approximately equipotent, whereas simvastatin is at least twice as effective per milligram of drug administered as lovastatin and pravastatin [1,2]. The side-effect profiles of the statins appeared similar, however, only lovastatin, pravastatin, and simvastatin have been subjected to long-term, large-scale, double-blind clinical trials. Earlier reports suggesting a higher incidence of sleep disorders in patients treated with lovastatin and simvastatin, compared with pravastatin, are not supported by more recent, controlled clinical trials [6].

Recently completed primary and secondary intervention trials have shown that the significant reductions in LDL-C achieved with simvastatin result in significant reductions in morbidity and mortality associated with CHD as well as reductions in the incidence of stroke and total mortality [4,7-10]. Such benefits occur early in the course of therapy and have led to suggestions that this drug may possess antiatherogenic effects over and above its capacity to lower atherogenic lipids and lipoproteins [11]. Some studies have also shown simvastatin-induced improvements in endothelial function [12], decreased platelet thrombus formation [13] and reduced frequency of transient myocardial ischemia [14]. Moreover, simvastatin is effective in lowering LDL-C levels in dyslipidemic diabetics [15,16].

Notably, the Scandinavian Simvastatin Survival Study (4S) is a prospective, randomized, multicenter

trial including 4,444 patients designed to test whether simvastatin (20-40 mg/day) could decrease all-cause mortality in patients with documented CHD [4]. Although noncardiac death rates were similar among the groups, the relative risk of mortality from any cause was decreased 30% and the relative risk of coronary mortality was decreased 42% in the simvastatin group [4]. Regarding the long-term safety of simvastatin, the only serious drug-related adverse effect during the 5.4-year median follow-up period was a single case of myopathy, which supports the excellent safety profile of simvastatin over 5 years [4].

The present study was undertaken to confirm and extend the results of a pilot study suggesting that Turks were more sensitive to the lipid-modulating effects of simvastatin than western Europeans [17]. In terms of the coronary risk profile. Turkish adults have some distinctive features such as comparatively low levels of plasma total cholesterol [18] and LDC-C [19], high levels of plasma triglycerides, and strikingly low levels of HDL-C [19,20], associated with elevated hepatic lipase [21]. Hypertension, physical inactivity and diabetes are prevalent in both genders, while smoking is common among men and obesity among women [22,23]. The participants in this study were characterized by very high total cholesterol and LDL-C values similar to those commonly seen in western populations but also in a minority of Turkish adults that should not be neglected.

In the current study an excellent overall mean decrease of 31.3% in LDL-C levels was attained with 10 mg/day of simvastatin. The percent change values for TC, TG, and HDL-C were -23.1%, -4.5% and 5.1%, respectively. The decline in LDL-C tended to be greater when the pretreatment values were higher. An excellent response was obtained, particularly in women, namely a reduction of LDL-C by 37% from a mean of 214 mg/dl and an increase of HDL-C by 7% to 51 mg/dl (Table 3). In addition, there was no effect of CHD and smoking status on the percent changes in LDL-C levels. The sensitivity to simvastatin may be related to extrinsic ethnic factors including social and cultural aspects (medical practice, diet, use of tobacco or alcohol, socio-economic status and compliance with prescribed medications) or to intrinsic factors of genetic polymorphism, age, gender, height, weight and organ dysfunction. Specifically, the Turks are unique in having an (25% increase in hepatic lipase that may modulate their responsiveness to lipid-lowering therapy [21]. Among other parameters studied, pulse rate, systolic and diastolic blood pressures did not change, while the significant reductions in mean body weight and BMI observed might be attributed to the efficacy of compliance of the subjects to the dietary restriction.

Previously, in an eight-week, placebo-controlled, multicenter, dose-response study, the efficacy of various dose levels of simvastatin (2.5, 5, 10, 20, and 40 mg) were evaluated in patients with hypercholesterolemia [24]. There was a significant linear dose response with regard to the decrease in LDL-C, TC and TG. Of interest, the increase in HDL-C and reduction in TC were statistically at doses of simvastatin greater than 5 mg, a trend we also documented with low-dose simvastatin in the current study. Furthermore, it has been estimated that doubling the dose of a statin leads to an additional reduction of LDL-C by 6% [25]. In view of the fact that a reduction of LDL-C by 35% had been attained with a mean dose of 27 mg of simvastatin in the 4S study [4], it would be reasonable to deduce that a 31% reduction would be achieved in a Scandinavian population with a daily simvastatin dose of 17 mg, a result obtained among Turks with 10 mg. Thus, the Turkish population does appear to be more sensitive to simvastatin, achieving a LDL-C reduction at a dose 41% less than that required for a comparable LDL-C decrease in the Scandinavian population.

The impact of statins on HDL-C levels is especially important because of the very low HDL-C in Turks [19,20]. In the present study there was a 5.1% increase in HDL-C levels, rather typical of many statin trials. However, recent data suggest that simvastatin may have an unexpected, unique effect on HDL-C levels, specifically in subjects with HDL-C<35 mg/dl, a value commonly seen in Turks. For example, in the CURVES study, simvastatin (40 mg per day) raised HDL-C levels an average of 9.6%, fluvastatin (40 mg per day) reduced HDL-C by 3% and atorvastatin (80 mg per day) reduced HDL-C by 0.1% [25].

In a study of 846 patients with baseline triglycerides of 186 mg/dl, LDL-C of 213 mg/dl, and HDL-C of 46 mg/dl (almost precisely the lipid profile of the

Turkish women in our study) the effects of equipotent doses of simvastatin and atorvastatin were compared [26]. Both statins resulted in the expected marked reduction in LDL-C. Simvastatin (40 or 80 mg per day) increased HDL-C by 6-7% and atorvastatin (20 or 40 mg per day) increased HDL-C by 3-4%. However, in subjects with HDL-C<35 mg/dl, simvastatin (80 mg per day) increased HDL-C by 17% and atorvastatin (40 mg per day) increased HDL-C by 7%. In an additional study, simvastatin has been shown to have a greater effect on HDL-C and apolipoprotein A-1 [27].

In a previous pilot study of 9 Turkish men with very low HDL-C levels (mean of 31 mg/dl), simvastatin (10 mg per day) resulted in a 20% increase in HDL-C levels [17]. In the present study, although subgroup analyses are limited by the small numbers of participants, there is a definite trend suggesting that Turkish men and women with the lowest HDL-C levels have an enhanced response to simvastatin (Table 4). Larger studies will be required to document accurately the magnitude of the increased HDL-C levels in Turks with low HDL-C in response to simvastatin, and head-to-head studies will be required to determine if the sensitivity of Turks to simvastatin is a class effect or unique to simvastatin.

In the present study, possible adverse drug-related side-effects were seen in eight (9.3%) patients and were considered to be of mild to moderate intensity. The drug was generally well tolerated at the dose studied, and treatment was discontinued in only two (2.3%) patients. Though there were mild elevations in serum creatinine, uric acid, AP, ALT and CK levels, the mean values of these laboratory variables were statistically similar compared to baseline. Some trials have reported myopathy [28] and persistent AST elevations [29] as dose-specific side-effects at higher doses of simvastatin (80 mg/dl). We did not observe myopathy or AST elevation at the low dose of simvastatin used in this trial.

We conclude that in Turkish patients with severe hypercholesterolemia, a mean decrease of 31% in LDL-C levels obtained with 10 mg of simvastatin is comparable to previous studies utilizing simvastatin at doses of approximately 20 mg in other populations. Furthermore, no significant side effects were observed. These findings suggest a unique increased susceptibility of Turkish adults to simvastatins, but indicate that the safety profile is similar to that of other nationalities.

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