Related Factors of Meeting National Cholesterol Education Program-recommended Goals with Atorvastatin

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The aim of this study was to observe the efficacy of atorvastatin and the related factors of meeting the National Cholesterol Education Program (NCEP)-recommended low-density lipoprotein (LDL) cholesterol levels in patients with hypercholesterolemia. A total of 107 patients were treated with atorvastatin 10 mg/day for 12 weeks. Eighty % of the patients achieved the target goals. There was a significant difference in the initial body mass index (BMI) between patients achieving the target goals and those not achieving the target goals ($p < 0.05$). In multiple stepwise logistic regression analysis, initial BMI and complications correlated with reaching the NCEP-recommended target goals ($p < 0.05$). A great number of patients treated with atorvastatin, including those previously poorly controlled with other therapies, reached the target goals at the starting dose 10 mg/day. BMI may be a useful index of achieving the NCEP-recommended target goals with atorvastatin. *J Atheroscler Thromb*, 2003; 10: 19-24.

Key words: Atorvastatin, Body mass index, National Cholesterol Education Program

Introduction

Various genetic and environmental factors contribute to the development and progression of atherosclerotic disease. The importance of hypercholesterolemia as a risk factor for coronary artery disease and the ability of cholesterol-lowering drugs to reduce the incidence of coronary heart disease or delay its progression is well established (1, 2). In 1993, the Adult Treatment Panel (ATP-II) report of the National Cholesterol Education Program (NCEP) outlined an updated systematic clinical approach to treating high blood cholesterol in adults (3). The expert panel recommends lipid-lowering drug treatment if, after an attempt at dietary intervention, low-density lipoprotein (LDL)

cholesterol remains ≥ 4.80 mmol/l in patients with less than 2 coronary heart disease (CHD) risk factors or ≥ 4.13 mmol/l in patients with 2 or more CHD risk factors. However, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors such as pravastatin and simvastatin have a rather limited capacity for lowering LDL cholesterol levels (4-6). Atorvastatin is a HMG-CoA reductase inhibitor that has been shown to lower LDL cholesterol 41% to 60% over its effective dose range (7, 8). We assessed the percentage of patients administered with atorvastatin reaching the NCEP-recommended target goals and its relational factors in patients with primary hypercholesterolemia and mixed hypercholesterolemia.

Methods

Patient selection

Patients with primary hypercholesterolemia and mixed hypercholesterolemia entered this open-label, observational study at four primary care centres in Shizuoka, Ja-

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pan. Eligible patients were aged 18 to 85 years with body mass index (BMI) $< 35 \text{ kg/m}^2$. The inclusion criteria were plasma LDL cholesterol $> 4.14 \text{ mmol/l}$ and plasma triglycerides (TG) below 4.52 mmol/l . Patients on lipid-lowering medication were allowed to participate if they met the inclusion criteria during treatment. We did not have a washout period. Patients were ineligible if they had active liver disease, or hepatic or renal dysfunction. Women with childbearing potential were also ineligible. Study participants could not concurrently take drugs known to affect lipid levels or known to interact with the study medication.

The enrolled patients started initial treatment of hyperlipidemia (Group I) or had taken a lipid-lowering drug previously (Group II). In group II, most (95 %) were receiving statins, whereas 4% were receiving fibrates and 1 % other drugs. All the previous drugs were replaced with atorvastatin. The detailed entry criteria for the study was 1) LDL cholesterol $\geq 4.80 \text{ mmol/l}$ in patients without CHD and with fewer than two risk factors as described by the NCEP-ATP II, 2) LDL cholesterol $\geq 4.13 \text{ mmol/l}$ in those without CHD and with two or more risk factors, or 3) LDL cholesterol $\geq 3.36 \text{ mmol/l}$ in those with CHD (3). Eligible patients were administered a fixed dose of atorvastatin 10 mg per day. Patients were required to adhere to the NCEP Step I diet or a similar diet during the follow-up period.

The target goals of therapy were to reduce LDL cholesterol to: 1) 4.13 mmol/l or less if fewer than two other risk factors without CHD were present, 2) 3.36 mmol/l or less if two (or more) risk factors without CHD were present, or 3) 2.59 mmol/l or less if CHD were present (3). Obesity was measured in terms of initial BMI before treatment. It was dichotomized with 25 kg/m^2 as the cutoff point (9). The objectives and implications of the study were explained to the patients according to the Declaration of Helsinki.

Laboratory methods

Fasting blood samples were drawn at the baseline and after 12 weeks of treatment for all lipid analyses. Patients in group II underwent laboratory examinations while taking their previous drugs. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and TG were measured by enzymatic methods. LDL cholesterol was estimated by the formula (LDL cholesterol = total cholesterol - HDL cholesterol - $\text{TG} \times 0.2$ [10]).

Efficacy and safety evaluation

At each visit, patients were asked about their health status and adverse events, and investigators assessed these events in terms of intensity, duration, relation to study medication, and clinical outcome. A full clinical laboratory evaluation (routine hematology and blood chemistry testing) was done at screening and 12 weeks, while safety evaluations (alanine aminotransferase, aspartate ami-

notransferase and creatine phosphokinase) were performed during the study period. Adverse events were recorded at each clinic visit. Associated adverse events were those the investigator judged definitely, probably or possibly related to treatment as well as those for which the investigator indicated an unknown relationship to treatment or insufficient available information for evaluation.

Statistical Analysis

Data were expressed as the mean $\pm$ standard deviation (for normally distributed variables) and percentage (for categorical variables). The comparison of continuous variables between the groups was performed with the paired or unpaired Student's *t* test (two-tailed) for normally distributed data or the Mann-Whitney *U* test for the other data. Comparisons of categorical variables were made by χ^2 and Fisher exact tests as appropriate. Univariate logistic regression analysis was used to select the independent predictive factors for achieving target goals within the entire study population. The covariates examined included clinical characteristics (age, sex, initial BMI, risk factors, and complications), and pre-treatment lipid values (total cholesterol, LDL cholesterol, HDL cholesterol, and TG). Univariate predictors of achieving target goals with a *p* value < 0.05 were entered into a multivariate logistic regression model with stepwise selection. Differences were considered statistically significant at a value of *p* < 0.05 .

Results

Patients

A total of 107 patients (27 men, 80 women) were treated with atorvastatin 10 mg/day; 33 with less than 2 risk factors and 63 with 2 or more risk factors. Eleven patients had CHD (Table 1). The mean age was 63 ± 11 years with 28 % of the patients ≥ 70 years. Median initial BMI was 24.1 kg/m^2 , with a range of the group median values from 23.5 to 25.5 kg/m^2 .

Efficacy analysis

Mean percent reductions from the baseline in LDL cholesterol levels were 36 ± 20 %. TG levels decreased 6 ± 47 %, and HDL cholesterol levels increased 3 ± 25 %. Age, sex, initial BMI, risk factors, and complications did not differ between Group I and Group II (Table 1). There were significant differences in total cholesterol levels and LDL cholesterol levels between the 2 groups before treatment.

There was a significant difference in initial BMI between patients achieving the target goals and those not achieving the target goals (*p* < 0.05) (Table 2). LDL cholesterol levels before and after treatment in patients achieving the target goals were lower than in those not achieving the target goals (*p* < 0.001).

Table 1. Clinical Characteristics and lipid values between the 2 groups

	All patients (n = 107)	Starting treatment group (Group I)(n = 38)	Previous treatment group (Group II)(n = 69)
Age (years)	63 ± 11	63 ± 10	63 ± 11
Sex (M/F)	27/80	8/30	19/50
Initial BMI (kg/m ²)	24.1 ± 3.5	23.8 ± 3.4	24.3 ± 3.5
Risk factors			
Hypertension	61 (57)	21 (55)	43 (62)
Diabetes Mellitus	25 (23)	11 (29)	14 (20)
Smoking	12 (11)	4 (11)	8 (12)
Complications			
Angina pectoris	8 (7)	3 (8)	5 (7)
Myocardial infarction	3 (3)	1 (3)	2 (3)
Lipid values before treatment			
Total cholesterol (mmol/l)	6.98 ± 0.81	7.33 ± 0.94**	6.79 ± 0.67
LDL cholesterol (mmol/l)	4.53 ± 0.75	4.77 ± 0.87***	4.40 ± 0.65
HDL cholesterol (mmol/l)	1.58 ± 0.48	1.63 ± 0.42	1.55 ± 0.51
Triglycerides (mmol/l)	1.97 ± 1.03	2.12 ± 1.06	1.88 ± 1.00
Lipid values after 12 weeks			
Total cholesterol (mmol/l)	5.24 ± 1.09	4.95 ± 0.80***	5.40 ± 1.20
LDL cholesterol (mmol/l)	2.93 ± 1.07	2.63 ± 0.76***	3.10 ± 1.18
HDL cholesterol (mmol/l)	1.56 ± 0.43	1.57 ± 0.40	1.56 ± 0.45
Triglycerides (mmol/l)	1.71 ± 1.03	1.67 ± 0.95	1.73 ± 1.07

Values are expressed as mean ± SD or number (%) of patients.

* $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$ vs previous treatment group.

BMI = body mass index; LDL = low-density lipid; HDL = high-density lipid

Table 2. Clinical Characteristics and lipid values between the 2 groups with or without meeting the target goal

	Achieving target (n = 86)	Not achieving target (n = 21)
Age (years)	63 ± 10	61 ± 13
Sex (M/F)	20/66	7/14
Initial BMI (kg/m ²)	23.7 ± 3.4***	25.7 ± 3.3
Previous lipid-lowering drugs	51 (59)	16 (76)
Risk factors		
Hypertension	51 (59)	12 (57)
Diabetes Mellitus	18 (21)	5 (24)
Smoking	9 (10)	3 (14)
Complications		
Angina pectoris	6 (7)	2 (10)
Myocardial infarction	2 (2)	1 (5)
Lipid values before treatment		
Total cholesterol (mmol/l)	6.91 ± 0.68***	7.34 ± 1.18
LDL cholesterol (mmol/l)	4.41 ± 0.64*	5.05 ± 0.93
HDL cholesterol (mmol/l)	1.61 ± 0.51	1.43 ± 0.34
Triglycerides (mmol/l)	1.98 ± 1.03	2.00 ± 1.06
Lipid values after 12 weeks		
Total cholesterol (mmol/l)	5.03 ± 0.65*	6.10 ± 1.88
LDL cholesterol (mmol/l)	2.68 ± 0.59*	3.93 ± 1.78
HDL cholesterol (mmol/l)	1.60 ± 0.45	1.41 ± 0.32
Triglycerides (mmol/l)	1.70 ± 1.03	1.74 ± 1.06

Values are expressed as mean ± SD or number (%) of patients.

* $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$ vs not achieving target group.

BMI = body mass index; LDL = low-density lipid; HDL = high-density lipid

Subgroup analysis

Before treatment, there were no significant differences in total cholesterol, LDL cholesterol, and HDL cholesterol levels between the overweight subjects (initial BMI ≥ 25 kg/m²) and lean subjects (initial BMI < 25 kg/m²) (Table 3). TG levels before treatment tended to be higher in overweight subjects than in lean subjects, but not significantly ($p = 0.06$). However, TG levels after 12 weeks differed between the 2 groups ($p < 0.05$). A significant greater percentage of lean subjects achieved the target goal compared with overweight subjects.

Univariate and multivariate logistic regression analysis

By univariate logistic regression analysis, initial BMI and complications were significant variables for reaching the NCEP-recommended target goals (Table 4). LDL cholesterol levels before treatment did not contribute to reaching the NCEP-recommended target goals. In multiple stepwise logistic regression analysis, those 2 parameters correlated with reaching the NCEP-recommended target goals.

Safety

All patients completed the study for 12 weeks. None of the serious adverse events (hospitalization, cancer, overdose, and death) were considered associated treatment. Four of the 107 patients were withdrawn. There were 2

patients with mild elevations (two to three times the reference range) of transaminase. Only one patient expressed persistent transaminase elevations greater than 3 times the upper limit of the normal range. One patient showed arthralgia. No patient had elevations of creatine kinase greater than 10 times the upper limit of normal.

Discussion

Obesity is frequently associated with insulin resistance and abnormal glucose homeostasis. Tumor necrosis factor- α plays an important role in mediating the insulin resistance of obesity through its overexpression in fat tissue (11). A recent study in an animal model indicated that chronic hyperinsulinemia reduces antilipolysis by downregulating mRNA for insulin receptor substrate-2, an essential component of the insulin-signaling pathway in liver, and activates fatty acid synthesis (12). Insulin-resistance associated with compensatory hyperinsulinemia is frequently linked to hypertriglyceridemia. In our study, triglycerides after treatment were still higher in overweight subjects. Further studies are required to clarify the relationship between the LDL cholesterol lowering efficacy of atorvastatin and hyperinsulinemia.

Alternatively, obesity was associated with an increased cholesterol synthetic rate equal to 20 mg/day for each

Table 3. Clinical Characteristics and lipid values between overweight subjects and lean subjects

	Lean subjects (<i>n</i> = 66)	Overweight subjects (<i>n</i> = 41)
Age (years)	63 $\pm$ 11	63 $\pm$ 9
Sex (M/F)	18/48	9/32
Initial BMI (kg/m ²)	22.1 $\pm$ 2.1**	27.5 $\pm$ 2.5
Risk factors		
Hypertension	35 (53)	29 (71)
Diabetes Mellitus	15 (23)	10 (24)
Smoking	9 (14)	3 (7)
Complications		
Angina pectoris	4 (6)	4 (10)
Myocardial infarction	1 (2)	2 (5)
Lipid values before treatment		
Total cholesterol (mmol/l)	6.97 $\pm$ 0.72	7.00 $\pm$ 0.96
LDL cholesterol (mmol/l)	4.53 $\pm$ 0.66	4.53 $\pm$ 0.89
HDL cholesterol (mmol/l)	1.62 $\pm$ 0.50	1.52 $\pm$ 0.44
Triglycerides (mmol/l)	1.86 $\pm$ 1.03	2.14 $\pm$ 1.01
Lipid values after 12 weeks		
Total cholesterol (mmol/l)	5.11 $\pm$ 0.76	5.46 $\pm$ 1.46
LDL cholesterol (mmol/l)	2.82 $\pm$ 0.73	3.11 $\pm$ 1.45
HDL cholesterol (mmol/l)	1.61 $\pm$ 0.46	1.49 $\pm$ 0.37
Triglycerides (mmol/l)	1.54 $\pm$ 1.01*	1.98 $\pm$ 1.02
Reaching target goals	57 (86)*	27 (66)

Values are expressed as mean $\pm$ SD or number (%) of patients.

* $p < 0.05$, ** $p < 0.001$ vs overweight subjects.

BMI = body mass index; LDL = low-density lipid; HDL = high-density lipid

Table 4. Univariate predictors of achieving the target goals

	Univariate coefficient	Standard error	P value
Age	-0.002	0.003	0.396
Sex	-0.053	0.078	0.498
Initial BMI	-0.229	0.010	0.026
Previous treatment	-0.135	0.089	0.133
Previous drugs	-0.006	0.011	0.584
Diabetes Mellitus	-0.006	0.077	0.460
Hypertension	0.066	0.067	0.333
Smoking	0.057	0.023	0.871
Complications	-0.404	0.097	0.001
Total cholesterol levels at baseline	0.001	0.003	0.867
LDL cholesterol levels at baseline	-0.005	0.004	0.124
HDL cholesterol levels at baseline	-0.001	0.001	0.535
Triglycerides levels at baseline	-0.002	0.003	0.627

BMI = body mass index; LDL = low-density lipid; HDL = high-density lipid

kilogram of body fat (13). It is possible that the activity of the HMG-CoA reductase increases in overweight subjects. Although the pharmacological action was different, *Post hoc* analysis of the Helsinki Heart Study with gemfibrozil suggested that the decrease in LDL cholesterol levels was more pronounced in subjects with a BMI below the median value (14). Lean subjects may benefit more from atorvastatin treatment than overweight subjects.

Statins have consistent and acceptable safety profiles, as evidenced by their widespread exposure in currently marketed compounds: lovastatin, pravastatin, simvastatin, and fluvastatin (5, 15, 16). This study coincided with previous reports that clearly established atorvastatin as an efficacious HMG-CoA reductase inhibitor for lowering LDL cholesterol. Recently, aggressive LDL cholesterol reduction by atorvastatin has been associated with greater regression of the carotid intima media thickness measured by quantitative B-mode ultrasound in patients with familial hypercholesterolemia, compared with simvastatin (17).

Hunninghake *et al.* suggested that a significantly greater percentage (71%) of 10 mg once daily atorvastatin-treated patients achieved the NCEP-recommended target goals after 12 weeks of treatment (18), while another report revealed that 32% of 10 mg atorvastatin-treated patients achieved the NCEP-recommended target goals after 12 weeks in patients with documented atherosclerosis (19). The discrepancy was attributed to differences in patient selection. At week 12, 80% of patients with fixed doses of 10 mg once daily reached their NCEP-recommended target goals in this study. The excellent result of atorvastatin for achieving NCEP-recommended target goals may result in less combination therapy, a low discontinuation rate, and high compliance.

Among more than 4,000 patients treated with atorvastatin, persistent transaminase elevations greater than 3 times the upper limit of the normal range were re-

ported for 30 patients (0.7%) (20). There was a dose-related increase in the number of patients with mild elevations of transaminase (one to two times the reference range) (7). On the other hand, in a long term study with atorvastatin in which all patients were treated for a comparable period, no dosage-related increase in minor elevations was observed (8). Alanine aminotransferase elevations greater than 3 times the upper limit of the normal range were examined according to stratification by age, sex, height, alcohol consumption, BMI, and final LDL cholesterol level. None of these variables was related to the incidence of alanine aminotransferase elevations greater than 3 times the upper limit of the normal range (20). To date, whether more frequent adverse events occur as a result of increased LDL cholesterol reduction remains obscure.

The study did not consist of a dietary baseline phase in patients with previous lipid-lowering treatment. Therefore, we took note of whether patients given atorvastatin achieve the NCEP-recommended LDL cholesterol target goals.

In conclusion, atorvastatin, with its enhanced efficacy, provides adequate therapy for a large number of dyslipidemic patients, including those previously poorly controlled with other therapies. With atorvastatin therapy, patients may be able to achieve the NCEP-recommended target goals in a shorter period of time. BMI may be a useful index of achieving NCEP-recommended target goals with atorvastatin.

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