Efficacy of Atorvastatin in Treating High Risk Patients to Reach Low Density Lipoprotein-Cholesterol Goals: The Treat to Target (TTT-Israel) Study

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Abstract

Background: Hyperlipidemia is a major risk factor for coronary heart disease. Reducing low density lipoprotein-cholesterol can significantly reduce the risk of CHD, but many patients fail to reach the target LDL-C goals due to low doses of statins or low compliance.

Objectives: To treat high risk patients with atorvastatin in order to reach LDL-C goals (either primary or secondary prevention) of the Israel Atherosclerosis Society.

Methods: In this open-label study of 3,276 patients (1,698 of whom were males, 52%), atorvastatin 10 mg was given as a first dose, with follow-up and adjustment of the dose every 6 weeks. While 1,670 patients did not receive prior hypolipidemic treatment, 1,606 were treated with other statins, fibrates or the combination of both.

Results: After 6 weeks of treatment, 70% of the patients who did not receive prior hypolipidemic medications and who needed primary prevention reached target LDL-C levels. Interestingly, a similar number of patients who received prior hypolipidemic treatment (other statins, fibrates or both) and who did not reach the LDL-C treatment goals reached the LDL-C goals for primary prevention with atorvastatin. Only 34% of all patients who needed secondary prevention reached the ISA LDL-C target of 100 mg/dl. Atorvastatin proved to be completely safe; only two patients had creatine kinase elevation above 500 U/L, and another six had mild CK elevation (< 500 U/L). None of the patients had clinical myopathy, and only one had to be withdrawn from the study.

Conclusion: Atorvastatin is a safe and effective drug that enables most patients requiring primary prevention to reach LDL-C goal levels, even with a low dose of 10 mg. Patients in need of secondary prevention usually require higher doses of statins.

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Low density lipoprotein is a key element in the pathogenesis of atherosclerosis and atherosclerotic vascular disease. Reduction of LDL-cholesterol reduces the morbidity and mortality of patients with hyperlipidemia [1–4]. The Israel Atherosclerosis Society published its guidelines in 2000 [5], and the following year the U.S. National Cholesterol Education Program published new guidelines for the treatment of patients with atherosclerosis and atherosclerotic vascular disease [6]. Both advocate the need to reach LDL-C target levels below 160, 130 and 100 mg/dl according to the number of risk factors or illnesses.

Despite the guidelines for primary and secondary prevention, recent studies show that adherence to these guidelines are far from desirable [7–13]. Schectman and Hiatt [7] studied the rate of LDL-C target goal achievement in a specialized lipid clinic and found that only 55% of the patients reached the NCEP recommended target LDL for primary and secondary prevention. The authors also stated that several factors contribute to the success rate in treating hyperlipidemia, namely high baseline LDL and triglyceride levels (both being predictors of failure), and a combination of hyperlipidemia medications. Marcelino and Feingold [8] found that only 33% of patients on statin monotherapy reached target LDL-C goals, and that most of the patients did not receive appropriate doses of statins.

The HERS research group [9] published data on the adherence to the NCEP goals in postmenopausal women with coronary artery disease across the United States. They found that 53% of the women did not receive any anti-hyperlipidemic medication and that 91% of all the volunteers enrolled in the study did not reach the recommended LDL target of < 100 mg/dl [9]. Another study documenting the rate of achieving LDL target goals is the L-TAP study [10], which found that only 18% of the patients in need of secondary prevention who visited the general practitioner's office reached the LDL target goal of < 100 mg/dl.

The causes of this problem were investigated [14] and we now know that it is a combination of several factors, including low compliance, insufficient dosage of statins, low efficacy of medication, and lack of follow-up and dose adjustment by the physician.

In the present study, we administered atorvastatin (Lipitor, Neopharm Ltd), a potent statin with the ability to reduce LDL-C, at a dose of 10 mg/day to reduce LDL-C to recommended target levels.

Patients and Methods

Patients and study design

Patients with LDL-C levels above the recommended target levels for primary and secondary prevention were included in this open-label prospective study. Patients were recruited in general practitioners' offices and in specialized lipid clinics in Israel. The Helsinki committee approved the study. Patients were included in the study if they met one or more of the following criteria:

CHD = coronary heart disease
LDL-C = low density lipoprotein-cholesterol
ISA = Israel Atherosclerosis Society
CK = creatine kinase

a) Patients with lipid levels above the IAS guidelines who did not receive hypolipidemic medications
b) Patients with LDL-C levels above the IAS guidelines despite treatment with other medications
c) Patients with triglyceride levels above the IAS guidelines despite treatment with other medications
d) Patients receiving a combination of hypolipidemic medications that were switched to atorvastatin monotherapy
e) Patients who suffered from side effects from other hypolipidemic medications.

Exclusion from the study included the following criteria:

a) Significant liver function abnormalities (alanine and aspartase aminotransferase levels threefold higher than normal)
b) Creatine phosphokinase elevation (> 220 IU)
c) Known sensitivity to atorvastatin
d) Pregnant women
e) Renal failure (creatinine > 1.5 mg/dl).

All patients underwent a complete lipid profile and liver and kidney function tests at the beginning of the study. Patients were then given atorvastatin at a dose of 10 mg/day and were asked to come for a follow-up visit 6 weeks later, at which time a survey for side effects and another lipid profile and liver and kidney function tests were performed.

Methods

The primary care physicians ordered the lipid measurements, which were measured at the different laboratories of the different health maintenance organizations (Maccabi, Leumit, Meuhedet and Klalit health services in every district).

Data management and statistical analysis

The results were analyzed using the SPSS 9.0 statistical software for windows. We used the paired *t*-test to compare the significance of the lipid levels, CPK, and liver function test changes before and after the intervention. Chi-square was used to compare the differences in the rate of target goal achievement.

Results

The study group comprised 3,289 patients of whom 1,698 were males (51.6%). The majority of patients were recruited in the general practitioner's office. Most of the patients (1,661, 50.7%) did not receive any hypolipidemic medication prior to inclusion. Other reasons for inclusion in the study were: not reaching target LDL levels (n = 1,237 patients, 37.6%); not reaching target triglyceride levels (n = 812, 24.7%); adverse reactions to other hypolipidemic medications (n = 115, 3.5%); and switching to monotherapy instead of combination hypolipidemic medications (n = 89, 2.7%).

Seventy-two percent of the patients were at an age considered a risk factor (> 45 years for men and > 55 years for women). Other risk factors were hypertension (54%), current smoking (24%), positive family history for ischemic heart disease (40%), and high density lipoprotein-cholesterol < 35 mg/dl (19%). Figure 1 presents the distribution of risk factors. Among the patients included in the study, 1,566 (47.6%) were in need of primary prevention, of whom 963 (61.5%) had two or more risk factors; and 1,723 (52.4%) had a target LDL-C of < 100 mg/dl (due to diabetes or secondary prevention) [Figure 1].

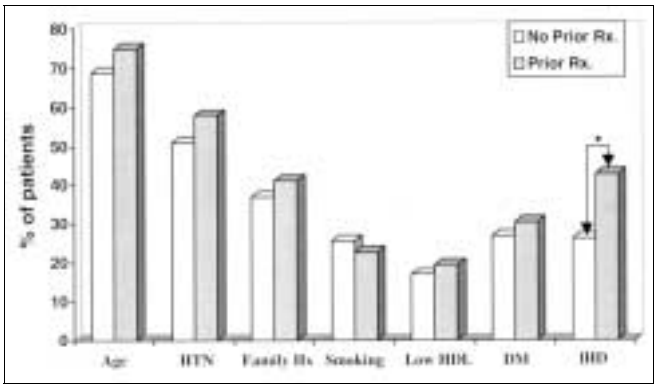

Figure 1. Risk factor distribution and diseases affecting IAS guidelines for target LDL. Patients are categorized into two groups according to previous medical treatment. There was no difference in the prevalence of risk factors between patients who did or did not take medication. Age: over 45 in males and over 55 in females. HTN = hypertension, Family Hx. = family history for ischemic heart disease, Smoking = current smokers (up until 6 months), Low HDL = HDL levels < 35 mg/dl at inclusion, DM = diabetes mellitus type II, IHD = ischemic heart disease.

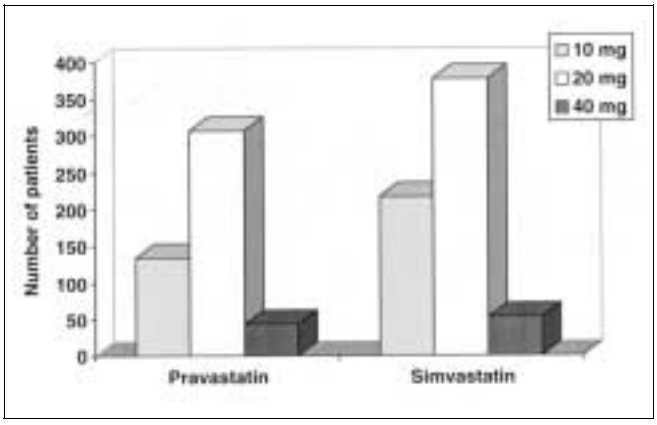

Figure 2. Number of patients receiving prior statin treatment and enrolled in the TTT study. Mean dose of simvastatin and pravastatin for patients receiving this prior statin treatment was 19.3 mg/day for both simvastatin and pravastatin.

Of the patients who had received prior statin treatment (1,163 patients, 35.4%), most (97%) took either simvastatin or pravastatin. The statin doses are shown in Figure 2; since fluvastatin, lovastatin and cerivastatin were given to only a minority of patients (< 3%), they are omitted from the figure. Most patients had received a statin dose of 20 mg/day (either simvastatin or pravastatin), and the mean dose was 19.7 mg/day for both statins [Figure 2].

Treatment with atorvastatin led to a significant improvement in lipid profile [Table 1]: total cholesterol was reduced by 22%, LDL-C

NCEP = National Cholesterol Education Program
CPK = creatine phosphokinase

Table 1. Lipid profile of patients before and after treatment with atorvastatin 10 mg/day

	Target LDL-C 160 mg/dl		Target LDL-C 130 mg/dl		Target LDL-C 100 mg/dl		All patients	
	Before	After	Before	After	Before	After	Before	After
All patients								
Total cholesterol (mg/dl)	272±39	208±37	267±43	205±36	255±46	200±39	261±44	203±38
LDL-C (mg/dl)	185±37	129±32	176±39	125±32	166±37	120±33	172±38	123±33
HDL-C (mg/dl)	46.4±12.9	48.6±12.6	43.8±12.9	46.2±12.1	42.3±12.5	44.9±11.9	43.5±12.8	46.0±12.2
No previous treatment								
Total cholesterol (mg/dl)	266±37	210±41	258±43	207±35	250±47	200±37	254±45	203±37
LDL-C (mg/dl)	177±40	129±37	167±38	125±32	160±39	119±32	164±39	122±33
HDL-C cholesterol (mg/dl)	48.712.8	50.1±13.8	44.7±13.3	46.4±12.6	41.9±12.4	44.4±12.0	43.6±12.9	45.7±12.5
Triglycerides (mg/dl)	208±104	170±81	231±118	181±75	232±123	18485	229±120	182±82
Previous statin treatment								
Total cholesterol (mg/dl)	266±38	210±41	258±42	208±34	251±48	202±38	255±46	204±38
LDL-C (mg/dl)	177±41	129±36	167±37	125±32	161±39	120±33	164±39	123±33
HDL-C (mg/dl)	49±13	50±14	45±13	47±13	42±13	45±12	44±13	46±12
Triglycerides (mg/dl)	199±98	161±70	228±113	177±72	227±116	182±85	224±114	178±80
Previous fibrate treatment								
Total cholesterol (mg/dl)	266±35	214±44	257±47	204±37	246±48	194±32	251±47	199±36
LDL-C (mg/dl)	173±33	129±38	164±41	122±33	156±38	113±29	160±39	117±32
HDL-C (mg/dl)	48±15	49±16	43±14	42±12	39±11	41±11	41±13	42±12
Triglycerides (mg/dl)	267±120	216±111	264±159	210±80	282±148	225±110	275±148	220±103

Data are given as mean ±SD and patient groups are categorized according to the IAS recommended guidelines.
Differences between "after" and "before" are highly significant in all groups (P <0.0001).

levels by 28% and triglyceride levels by 22%. HDL-C levels increased by 5.7%. The improvement in the lipid profile was similar in patients who did not receive hypolipidemic medications prior to inclusion in the study: total cholesterol was reduced by 20%, LDL-C levels by 26%, and triglyceride levels by 21%. HDL-C levels increased by 5.7% [Table 1].

A total of 1,676 patients (51.0%) reached their ISA target LDL-C levels. In our study group, the lower the target levels the lower the percentage of patients reaching their target goals. Of the 603 patients (83.7%) with fewer than two risk factors, 505 reached LDL-C levels < 160 mg/dl; while 592 of the 963 patients (61.5%) with two or more risk factors reached LDL-C levels < 130 mg/dl. In total, 579 of 1,613 patients (35.9%) reached the designated LDL-C level of < 100 mg/dl. Of all patients in need of primary prevention, 70% (n = 1,097) reached the designated LDL-C level (either 160 or 130 mg/dl).

The safety of atorvastatin was shown to be high; only 7 patients (0.2%) had CK elevation > 500 U/L, and another 16 (0.5%) had mild CK elevation (< 500 U/L). None of the patients had clinical myopathy, and only one patient had to be withdrawn from the study (CPK level > 3,000). Liver function tests did not change significantly during the study period: 165 patients (5%) had mild liver enzyme elevation (less than three times the normal) at inclusion and did not necessitate withdrawal from the study. These values did not change throughout the study period.

Analysis of the factors that influenced the success rate of reaching the IAS LDL-C target levels shows that patients who had received previous hypolipidemic medications had a lower tendency to achieve their target levels. Thus, 924 (55.2%) of the patients who did not receive hypolipidemic medications reached the LDL-C target level, as compared to 752 (44.4%) who did receive prior hypolipidemic medication [Table 2]. Other factors influencing the achievement rate included the baseline LDL-C (the higher the baseline LDL, the lower the achievement rate) [Table 2].

Table 2. Success rate of reaching LDL-C target levels according to previous hypolipidemic medications and different parameters

	Previous statin treatment	No previous treatment	*P*	All patients
All patients	752 (44.4%)	924 (55.2%)	<0.01	1676 (51.0%)
Target LDL-C levels				
160 mg/dl	172 (82.4%)	333 (85.0%)	NS	505 (83.7%)
130 mg/dl	262 (60.3%)	330 (62.4%)	NS	592 (61.5%)
100 mg/dl	310 (33.9%)	269 (37.6%)	NS	579 (35.9%)
Baseline LDL levels				
< 130 mg/dl	185 (67.8%)	76 (73.1%)	NS	261 (69.4%)
131–160 mg/dl	222 (43.9%)	227 (60.9%)	<0.001	449 (51.0%)
161–190 mg/dl	170 (35.1%)	314 (51.3%)	<0.001	484 (44.2%)
> 190 mg/dl	98 (27.9%)	225 (38.5%)	=0.001	323 (34.5%)
Gender				
Male	361 (40.4%)	403 (49.7%)	NS	764 (44.8%)
Female	313 (43.5%)	441 (51%)	NS	754 (47.6%)

Discussion

Achievement of target LDL-cholesterol levels is one of the main goals in treating patients with atherosclerotic vascular disease. Despite this fact, new studies have shown that the rate of this achievement among patients in need of primary as well as secondary prevention is very low [6–12]. This low success rate can be attributed to several factors [9], including low patient

HDL = high density lipoprotein

compliance, low drug potency, and lack of follow-up on the lipid profile change after initiation of hypolipidemic treatment.

Follow-up by physicians of their patients' lipid levels has a major impact on the ability to reach target levels. In 1999, Sueta et al. [11] published data from the QAP (Quality Assurance Program), a U.S. nationwide endeavor to treat CHD patients. They found that 44% of the patients with ischemic heart disease did not have LDL levels noted in their clinic chart. Of all the patients who had a LDL measurement, only 25% had LDL levels < 100 mg/dl, and 65% of patients receiving statins did not have the dose adjusted from the starting dose.

We studied the effect of atorvastatin to achieve LDL-C target levels for primary and secondary prevention. Since atorvastatin is one of the most potent statins available today, we investigated the effect of 10 mg of this drug on the patients' lipid profile. We found that even a low dose of 10 mg enabled 70% of the patients to reach primary prevention levels of LDL-C (either 160 or 130 mg/dl according to the number of risk factors) after 6 weeks. These figures are corroborated by previous studies [13]. To reach LDL-C levels of < 100 mg/dl (for secondary prevention and diabetics), 10 mg atorvastatin proved to be insufficient as only 30% of the patients reached the recommended LDL-C level.

Several factors influenced the achievement of the recommended target LDL levels, particularly the baseline LDL-C prior to treatment. If the baseline LDL-C level was > 190 mg/dl, the success rate dropped to 34.5% [Table 2]. Gender did not affect the rate of achievement.

Our data suggest that previous hypolipidemic medication (either statins or fibrates) did not affect the success rate when patients were switched to atorvastatin. Previous statin treatment affected the success rate only in relation to the baseline LDL-C. If baseline LDL levels were above 160 mg/dl, despite anti-hyperlipidemic medications, the chance of achieving the target LDL level with 10 mg atorvastatin was reduced. However, we found that previous medication did not affect the success rate if baseline LDL-C was below 130 mg/dl, but we cannot rule out a type 2 error because of the relatively small number of patients in this specific group.

Since we did not design the study to compare atorvastatin with other statins available today, we cannot conclude that atorvastatin is more potent than others. However, it may be superior to some statins in terms of the therapeutic index (percent LDL decrease divided by statin dose), but we cannot assume that 10 mg of atorvastatin is superior to an increase in dosage of other statins already given, when trying to achieve the LDL target, or to an appropriate dose of fibrates in cases of hypertriglyceridemia.

We found that atorvastatin at a starting dose of 10 mg/day can effectively achieve the target LDL-C levels for primary prevention in patients with moderately elevated LDL-C (< 160 mg/dl). However, 10 mg atorvastatin is not enough for patients in need of secondary prevention or for those with marked LDL-C elevation (> 160 mg/dl). Treatment in this group of patients must start with a statin dose higher than the equivalent of 10 mg atorvastatin. For patients already receiving other statins and who failed to reach the LDL-C target, it is more logical to increase the dosage of the statin before changing the type.

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