Statins: An Effective Anti-Atherosclerosis Therapy

Ardon Rubinstein MD and Elena Izkhakov MD

Metabolic Institute, Sourasky Tel Aviv Medical Center, Tel Aviv, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: statins, atherosclerosis, low density lipoprotein-cholesterol, atorvastatin

IMAJ 2002;4:456–457

The isolation of a specific competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl COA reductase from the fungus *Aspergillus terreus* opened the way for the development of a new family of cholesterol-lowering agents called statins. These statins – atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin – are all available on the Israeli market. Their mechanism of action is to target hepatocytes and reduce cholesterol production by inhibiting HMG COA reductase, a rate-controlling enzyme that converts HMG-COA to mevalonic acid, which is a precursor of cholesterol synthesis. Reduction of cholesterol synthesis in the hepatocyte upregulates hepatic low density lipoprotein receptors, leading to increased removal of plasma LDL-C, intermediate density lipoprotein and very low density lipoproteins [1,2]. Statins reduce the production of apolipoprotein B and increase hepatic apolipoprotein-B/E receptors [3]. Apart from its hypocholesterolemic action, statins have few other anti-atherogenic properties.

Cholesterol-lowering by statins results in significant improvement in endothelial function, and reduces the frequency and intensity of ischemic episodes detected by 48 hour Holter monitoring [4]. The statins induce activation of the nitric oxide synthase gene in human endothelial cells [5], decrease smooth muscle growth *in vitro* [6], and reduce the proliferation of macrophages induced by oxidized LDL-C and its accumulation in the cells [7]. In addition, they may affect the cells' thrombus formation [8], lower the levels of C-reactive protein in the plasma [9], and eliminate the higher risk of cardiovascular events associated with this inflammatory factor.

An elevated LDL-C level is the key risk factor for coronary heart disease. Primary and secondary prevention trials have shown that the use of statins to lower LDL-C levels can substantially reduce coronary events, strokes, and death from coronary heart disease [Table 1].

Clinical studies have demonstrated that statins in addition to reduction of CHD morbidity and mortality increase survival in hypercholesterolemic and normocholesterolemic subjects.

The Scandinavian Simvastatin Survival Study (4S) [10] showed that reduction of cholesterol by simvastatin reduced all-cause mortality in CHD patients. In this study 4,444 CHD patients with elevated cholesterol levels of 212–310 mg/dl were treated with simvastatin for 5 years. Results showed that all-cause mortality was reduced by 30%, major coronary events by 34%, and coronary death

CHD = coronary heart disease

Table 1. Major clinical intervention trials of the effects of statins on mortality, coronary events and stroke

Trials [Ref]	Study description	Duration (yr)	LDL-C reduction (%)	Mortality reduction (%)	CAD death reduction (%)	Stroke reduction (%)
4S [10]	4,444 patients, HC, CAD, simvastatin 10–40 mg/day	5.0	35	30	42	30
WOSCOPS [11]	6,595 patients, HC, No CAD, pravastatin 40 mg/day	4.9	26	22 (NS)	33	11 (NS)
CARE [12]	4,159 patients, NC, CAD, pravastatin 40 mg/day	5.0	28	8 (NS)	19	31
AFCAPS/ TexCAPS [14]	6,605 patients, NC, No CAD, lovastatin	5.2	25	NA	36	NA
LIPID [13]	9,014 patients, NC, CAD, pravastatin 40 mg/day	6.1	25	22	24	19
HPS (15)	20,536 patients, NC, CAD, simvastatin 40 mg/day	5.5		12	24	27

HC = hypercholesterolemia, NC = normocholesterolemia, CAD = coronary artery disease, NS = not significant, NA = not available.

HMG = 3-hydroxy-3-methylglutaryl
LDL = low density lipoprotein

by 34%. In the West of Scotland Coronary Prevention Study (WOSCOPS) [11] – a primary prevention study conducted in 6,595 men with cholesterol levels of 272 mg/dl without CHD for 4.9 years – pravastatin 40 ng reduced non-fatal myocardial infarction rates by 31% and death from CHD and all-cause mortality by 22%. In the Cholesterol And Recurrent Events (CARE) [12] trial – a secondary prevention study in which 4,159 men and women with LDL-C levels of 115–174 mg/dl took 40 mg pravastatin for 5 years – MI and fatal coronary events were reduced by 19%. The Long-term Intervention trial with Pravastatin in Ischemic Disease study (LIPID) [13] compared 40 mg of pravastatin to placebo in 9,014 men and women who had CHD and cholesterol levels of 155–271 mg/dl. After 6.1 years all-cause mortality was reduced by 22%, CHD mortality by 24%, and stroke by 19%. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXAS) [14] of 6,605 men and women without CHD who had LDL-C levels of 130–190 mg/dl and HDL-C levels below 50 mg/dl, 40 mg lovastatin reduced LDL-C levels to below 110 mg/dl. After 4.8 years the incidence of first major acute coronary event was reduced by 36%. In the recent Heart Protecting Study (HPS) [15] in which 20,536 individuals with low LDL-C levels and a history of CHD, peripheral vascular disease or diabetes were treated for 5.5 years with 40 mg simvastatin, the overall mortality was reduced by 12%, CHD death by 24%, and stroke by 27%.

The results of these epidemiologic studies prompted the American Medical Association [16] and the Israel Medical Association [17] to elect a panel of experts to formulate guidelines for the treatment and prevention of ischemic heart disease and atherosclerotic vascular disease. These guidelines focus on cholesterol management and reduction of LDL-C to target levels, subject to existing risk factors and history of prior CHD.

In the current issue of *IMAJ*, Leibovitz et al. [18] report on their use of 10 mg atorvastatin to reach target levels of LDL-C and triglycerides in 3,289 patients. Their results show that 70% of primary prevention patients reached the LDL-C target, an achievement surpassing any previously published results, as well as a remarkably low rate of side effects (0.7% elevation of creatinine phosphokinase, no change in liver enzymes, and only one patient was withdrawn from the study). The reduction of triglycerides by 22% with 10 mg atorvastatin is also remarkable. Especially unusual results were found in the group of patients who were previously on filtrate therapy; their triglyceride levels of 275 mg/dl declined to 220 mg/dl after switching to 10 mg atorvastatin. We do not have any reasonable explanation for this drop in triglycerides using 10 mg atorvastatin. This large-scale study with its excellent results is extremely promising, despite its shortcomings of short duration and some unclear points in its methodology. We encourage others to continue the follow-up of this large group of patients which undoubtedly will furnish us with invaluable data in the coming years.

MI = myocardial infarction
HDL = high density lipoprotein

References

1. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;232:34–47.
2. Sehayek E, Butbul E, Avner R, et al. Enhanced cellular metabolism of very low density lipoprotein by simvastatin: a novel mechanism of action of HGM-Coa reductase inhibitors. *Eur J Clin Invest* 1994; 24:173–8.
3. Gaw A, Packard CJ, Murray EF, et al. Effects of simvastatin on apoB metabolism and LDL subfraction distribution. *Arterioscler Thromb* 1993;13:170–89.
4. Van Boven AJ, Jukema JW, Zwinderman AH, et al. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. *Circulation* 1996;94:1503–5.
5. Laufs U, Fata VL, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HGM CoA reductase inhibitors. *Circulation* 1998;97:1129–35.
6. Negre-Aminoux P, van Vliet AK, van Ercck M, van Thiel GC, van Leeuwen RE, Cohen LH. Inhibition of proliferation of human smooth muscle cells by various HMG-CoA reductase inhibitors: comparison with other human cell types. *Biochim Biophys Acta* 1997;1345:259–68.
7. Kempen HJM, Vermeer M, deWit E, Havekes LM. Vastatins inhibit cholesterol ester accumulation in human monocyte-derived macrophages. *Arterioscler Thromb* 1991;11:146–53.
8. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statin: implication for cardiovascular event reduction. *JAMA* 1998;279:1643–50.
9. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Brunwald E. Long term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 1999;100:230–5.
10. Scandinavian Simvastatin study group. Randomised trials of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Study (4S). *Lancet* 1994;344:1383–9.
11. Shepherd J, Cobbe SM, Ford I, et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333:1301–7.
12. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol And Recurrent Events trial investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–9.
13. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study group. Prevention of cardiovascular events and death with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–57.
14. Downs JR, Clearfield M, Weis S, et al., for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/ TexCAPS. *JAMA* 1998;279:1615–22.
15. Colins R. Heart Protection Study represented in the American Heart Association meeting, 13 Nov 2001.
16. Lauer MS, Fontanarosa PB. Updated guidelines for cholesterol management. *JAMA* 2001;285:2508–9.
17. Harats D, Rubinstein A, Pharan E, et al. The Israeli recommendations for treatment and prevention of ischemic heart disease and atherosclerotic vascular disease. *Harefuah* 2000;138:28–38 (Hebrew).
18. Leibovitz E, Harats D, Gavish D. Efficacy of atorvastatin in treating high risk patients to reach low density lipoprotein-cholesterol goals: the Treat to Target (TTT-Israel) Study. *IMAJ* 2002;4:407–10.

Correspondence: Dr. A. Rubinstein, Director, Metabolic Institute, Sourasky Tel Aviv Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel.
Phone: (972-3) 697-3415
Fax: (972-3) 697-4494
email: vaadrof@tasmc.health.gov.il