An Open-Label Comparison of the Effects of Simvastatin and Niacin Alone and Combined on the Lipid Profile and Lipoprotein (a) Level in an Indian Population with Dyslipidemia

Kirandeep Kaur, MD, Jaswant Rai, MD, Geeta Sharma, DA, MD,
and Baljinder Singh Bal, MD, FCCP, FICA, FIACM

*Departments of Pharmacology and Medicine, Government Medical College,
Amritsar (Punjab), India*

ABSTRACT

Background: Patients with dyslipidemia often require the use of >1 lipid-altering agent to achieve the target levels recommended by the National Cholesterol Education Program Adult Treatment Panel III.

Objective: The aim of this study was to compare the effects of simvastatin and niacin alone and combined on the lipid profile and lipoprotein (a) (Lp[a]) level in an Indian population with dyslipidemia.

Methods: This 12-week, open-label, nonrandomized study was conducted at the Departments of Pharmacology and Medicine, Government Medical College, Amritsar (Punjab), India. Patients aged 30 to 70 years with dyslipidemia were eligible. Patients were assigned to 1 of 3 treatment groups. Group 1 received simvastatin 20 mg/d for 12 weeks. Group 2 received niacin at doses of 375 mg/d for 1 week, 500 mg/d for 1 week, and 500 mg BID for 10 weeks. Group 3 received simvastatin 10 mg/d plus niacin (375 mg for 1 week and 500 mg for 11 weeks). The lipid profile (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglycerides [TG]) and Lp(a) were measured before the start of therapy and at 6 and 12 weeks of treatment. Percentage changes from baseline were calculated. Adverse effects (AEs) were recorded at weeks 6 and 12 and through spontaneous reporting.

Results: Ninety patients were enrolled (50 men, 40 women; 30 patients per treatment group). In group 1, the mean (SD) percentage decrease in LDL-C level at 12 weeks was 42.79% (16.29%) ($P < 0.05$), but no significant change was seen in group 2 or 3. The mean (SD) percentage increases in HDL-C level were 18.43% (13.28%) and 20.82% (17.57%) in groups 2 and 3, respectively (both, $P < 0.05$), but no significant change was seen in group 1. TC levels decreased by a mean (SD) of 32.97% (13.66%) in group 1 ($P < 0.05$), but no significant change was seen in group 2 or 3. TG and Lp(a) levels did not change significantly in any of the 3 treatment groups. Flushing, myalgia, and dyspepsia were the most common AEs in patients receiving niacin.

Conclusions: In this study in Indian patients with dyslipidemia, simvastatin-niacin combination therapy was associated with greater changes in lipid profile compared with either agent used alone. Niacin was also associated with greater changes in Lp(a) levels. AEs were less prevalent with combination therapy than with niacin alone. (*Curr Ther Res Clin Exp.* 2004;65:455–469) Copyright © 2004 Excerpta Medica, Inc.

Key words: dyslipidemia, simvastatin, niacin, combination therapy.

INTRODUCTION

A major new feature of the guidelines issued by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)¹ is a focus on primary prevention of coronary artery disease (CAD) in persons with multiple risk factors. Most patients at high risk for CAD are likely to benefit from intensive management. The ATP III report includes a modified list of risk factors and their management.¹ Now, a low-density lipoprotein cholesterol (LDL-C) level <100 mg/dL is considered optimal. The desired level of high-density lipoprotein cholesterol (HDL-C) has been raised from <35 mg/dL to <40 mg/dL. The triglyceride (TG) cutoff point has been lowered to 150 mg/dL. The ATP III report recognizes that the risk for CAD is also influenced by factors that are not included among the major independent risk factors. These include lifestyle (eg, lack of exercise, poor diet, smoking), elevated lipoprotein (a) (Lp[a]) level, elevated homocysteine level, and impaired glucose tolerance. ATP III also mentions management of the metabolic syndrome as a secondary goal of risk-reduction therapy, after the primary goal of decreasing LDL-C.

Because the NCEP has revised the target lipid levels, there is a need to reconsider the current treatment strategy for dyslipidemia. Of the various lipid-altering agents available, statins are the most commonly prescribed because of their beneficial effects on LDL-C and total cholesterol (TC) levels.² Niacin, another lipid-altering agent, improves HDL-C, TG,^{3–5} and Lp(a)⁶ levels. The use of niacin has decreased over the years because of the severe adverse effects (AEs) associated with it (eg, myalgias, hepatotoxicity, flushing). Now, however, a lower dose (1–2 g/d) of niacin is being considered for its effect on the lipid profile. In addition to monotherapy with a lipid-altering drug, the use of combination therapy is becoming increasingly important for effective management of dyslipidemia.

Another factor to consider when prescribing risk-reduction therapy is that lipid profiles in persons with dyslipidemia vary by race/ethnic group. For example, Indian patients with dyslipidemia typically have high TG and Lp(a) levels and a low HDL-C level,⁷ with moderately elevated LDL-C and TC levels. One study showed that a serum cholesterol level normal in the white population may be high for the Asian Indians.⁸ A study in Singapore showed that mean Lp(a) levels in Indians were higher among all of the ethnic groups except blacks.⁹

The present study was conducted to compare the effects of simvastatin and niacin alone and combined on dyslipidemia in an Indian population. Simvastatin

was chosen from the group of statins because, according to a MEDLINE search (key terms: *lipid-altering agents*, *dyslipidemia*, and *statins*; years: 2003–2004), most studies of risk reduction to date have focused on simvastatin.

PATIENTS AND METHODS

This 12-week, open-label, nonrandomized trial was conducted at the Departments of Pharmacology and Medicine, Government Medical College, Amritsar (Punjab), India. The study and the consent procedure were approved by the ethics committee at the Government Medical College.

Inclusion and Exclusion Criteria

Patients aged 30 to 70 years with dyslipidemia (defined as LDL-C >110 mg/dL, HDL-C <40 mg/dL, and/or TC >200 mg/dL) were eligible. Patients were recruited from an outpatient clinic at Guru Nanak Dev Hospital, adjacent to the Government Medical College.

Patients with the following conditions were excluded from the study: hypersensitivity to simvastatin or niacin; significant metabolic, renal, hepatic, or gastrointestinal disease; infection, gangrene, or surgery within the prior 3 months; history of myocardial infarction, unstable angina, or congestive heart failure; history of alcoholism; history of a convulsive disorder; hyperuricemia; diabetes mellitus; history of acute peptic ulcer disease; history of muscle pain (fibromyalgia) and an associated increase in creatine phosphokinase level; hypothyroidism; or history of hormone use. Pregnant and breastfeeding women were also excluded. The use of drugs such as verapamil, diltiazem, erythromycin, clarithromycin, ketoconazole, and itraconazole was not allowed during the study.

Eligible patients provided verbal informed consent after receiving a full explanation of the study procedures.

Study Drug Administration and Efficacy and Tolerability Assessments

After enrollment, patients provided a medical history; underwent a physical examination (including vital sign measurements and hemoglobin levels); and were assigned, based on physician discretion, to 1 of 3 treatment groups. Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. Group 2 received niacin (sustained release [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks.

During treatment, patients were advised to continue their earlier lipid-lowering diet and physical activity if they had already been doing so (although they were not instructed to begin these lifestyle changes for the purposes of the study). Lipid levels and liver enzymes (to monitor for adverse effects) were measured before the start of therapy (week 0) and at weeks 6 and 12 of treatment (study

end). Patients were advised to immediately report unexplained muscle pain or fatigue, low urine output, irritable bowel, and any other AE, whether thought to be caused by the study drug or by cardiovascular problems. At the end of therapy, patients were monitored for AEs for 4 to 6 additional weeks at the Departments of Pharmacology and Medicine.

Laboratory Procedures

Laboratory analyses were performed at weeks 0, 6, and 12. Blood samples were drawn after 12 hours of fasting and allowed to clot at room temperature. Serum was assayed by centrifugation at 2000 rpm for 10 minutes at 37°C and used to determine TC level, followed by HDL-C level after precipitation of very low-density lipoprotein (VLDL) and LDL-C with dextran sulfate magnesium chloride with use of the enzymatic cholesterol oxidase, para-aminophenazone peroxidase method^{10,11} (Biosystems kit, Biosystems Diagnostics, Spain). The serum TG level was determined by measurement of glycerol after enzymatic hydrolysis with lipase¹² (Biosystems kit). The LDL-C level was calculated using the following formula¹³:

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{VLDL}$$

Serum Lp(a) was measured using the turbidimetry method.¹⁴ Blood samples were analyzed using a spectrophotometer (Spectronic 20, Spectronic Analytical Instruments, Garforth, Leeds, United Kingdom). The lipid tetrad index (a comprehensive lipid index proposed to ascertain the total burden of dyslipidemia in Indians¹⁵) was calculated at weeks 0, 6, and 12 using the following formula:

$$\text{Tetrad index} = \text{TC} \times \text{TG} \times (\text{Lp[a]}/\text{HDL-C})$$

Statistical Analysis

The data were analyzed using the *t* test. *P* < 0.05 was considered statistically significant.

RESULTS

Ninety patients were enrolled (50 men, 40 women; 30 patients per treatment group) (Table I). All patients lived in the state of Punjab, India, with 60 (67%) from urban areas and 30 (33%) from rural areas. CAD risk factors present at baseline are shown in Table II.

Efficacy

Table III presents the mean lipid levels and percentage changes from weeks 0 to 12.

Figure 1 shows the mean serum LDL-C levels throughout the study. Group 1 had a significant decrease over 12 weeks (from 198.51 [55.62] mg/dL at baseline

Table I. Distribution of Indian patients (no. [%]) with dyslipidemia by baseline lipid levels.*

Lipid/Level, mg/dL	Group 1 [†] (n = 30)	Group 2 [‡] (n = 30)	Group 3 [§] (n = 30)
LDL-C			
≤100	0 (0)	10 (33)	0 (0)
>100–150	7 (23)	13 (43)	6 (20)
>150–200	9 (30)	7 (23)	10 (33)
>200	14 (47)	0 (0)	14 (47)
HDL-C			
≤40	10 (33)	21 (70)	16 (53)
>40	20 (67)	9 (30)	14 (47)
TC			
≤200	0 (0)	14 (47)	0 (0)
>200–250	11 (37)	11 (37)	8 (27)
>250–300	10 (33)	5 (17)	8 (27)
>300	9 (30)	0 (0)	14 (47)
TG			
≤150	9 (30)	4 (13)	3 (10)
>150–200	10 (33)	6 (20)	7 (23)
>200–250	5 (17)	12 (40)	11 (37)
>250	6 (20)	8 (27)	9 (30)
Lp(a)			
≤30	19 (63)	7 (23)	19 (63)
>30	11 (37)	23 (77)	11 (37)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; Lp(a) = lipoprotein (a).

*Percentages may not total 100 due to rounding.

[†]Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks.

[‡]Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks).

[§]Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks.

to 146.71 [36.49] mg/dL at week 6 [$P < 0.002$] to 106.57 [24.06] mg/dL at week 12 [$P < 0.001$]; mean [SD] percentage decrease, 42.79% [16.29%]). In group 2, no significant change was seen. In group 3, the decrease from baseline was significant at week 6 (from 210.47 [65.71] mg/dL to 143.84 [48.06] mg/dL; $P < 0.001$) but no significant change was seen at 12 weeks.

Mean serum HDL-C levels throughout the study are shown in **Figure 2**. In group 1, the increase from baseline to week 6 was significant (from 43.22 [2.90] mg/dL to 45.62 [2.93] mg/dL; $P < 0.014$), but no significant change was seen at week 12. Group 2 showed a nonsignificant increase from baseline to week 6 and

Table II. Baseline risk factors for coronary artery disease (CAD) in Indian patients with hyperlipidemia (no. [%]).

Risk Factor	Group 1* (n = 30)	Group 2† (n = 30)	Group 3‡ (n = 30)
Hypertension	22 (73)	24 (80)	25 (83)
Lp(a) >30 mg/dL	12 (40)	20 (67)	13 (43)
Family history of CAD	10 (33)	8 (27)	10 (33)

Lp(a) = lipoprotein (a).

*Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks.

†Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks).

‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks.

Table III. Lipid levels (mg/dL) and percentage changes in Indian patients before and after 12 weeks of therapy for hyperlipidemia. Data are mean (SD).

Lipid/Time Point	Group 1* (n = 30)	Group 2† (n = 30)	Group 3‡ (n = 30)
LDL-C			
Week 0	198.51 (55.62)	116.97 (38.86)	210.47 (65.71)
Week 12	106.57 (24.06) [§]	103.90 (27.88)	117.60 (40.76)
%Δ	42.79 (16.29)	5.47 (27.47)	42.50 (16.01)
HDL-C			
Week 0	43.22 (2.90)	39.64 (6.67)	41.05 (5.89)
Week 12	46.56 (2.72)	46.33 (3.94) [§]	48.53 (2.78) [§]
%Δ	7.95 (6.39)	18.43 (13.28)	20.82 (17.57)
TC			
Week 0	278.91 (50.76)	200.49 (38.22)	299.97 (61.91)
Week 12	184.49 (24.60) [§]	184.02 (24.61)	197.05 (38.51) [§]
%Δ	32.97 (13.66)	8.56 (12.97)	33.21 (11.51)
TG			
Week 0	183.76 (74.08)	235.81 (82.84)	242.95 (76.85)
Week 12	140.29 (48.66)	166.26 (50.57)	154.20 (45.68)
%Δ	20.44 (15.04)	26.89 (12.91)	34.11 (15.67)
Lp(a)			
Week 0	26.86 (19.84)	50.89 (31.44)	30.80 (29.79)
Week 12	18.54 (10.39)	26.45 (15.92)	18.52 (14.11)
%Δ	19.22 (22.29)	53.64 (21.56)	25.44 (23.58)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; Lp(a) = lipoprotein (a).

*Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks.

†Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks).

‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks.

[§]P < 0.05 versus week 0.

Figure 1. Mean (SD) low-density lipoprotein cholesterol (LDL-C) levels in Indian patients receiving treatment for dyslipidemia. *Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. †Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). ‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks. [§] $P < 0.05$ versus week 0.

a significant increase at week 12 (from 43.33 [4.95] mg/dL to 46.33 [3.94] mg/dL [$P = 0.04$]; mean [SD] percentage increase, 18.43% [13.28%]). In group 3, the increases from baseline to weeks 6 and 12 were significant (from 41.05 [5.89] mg/dL at baseline to 44.89 [3.15] mg/dL at week 6 [$P < 0.015$] to 48.53 [2.78] mg/dL at week 12 [$P < 0.001$]; mean [SD] percentage increase, 20.82% [17.57%]).

Figure 3 shows the mean TC levels in the 3 treatment groups. Group 1 showed a significant decrease from baseline to weeks 6 and 12 (from 278.91 [50.76] mg/dL at baseline to 223.01 [34.85] mg/dL at week 6 [$P < 0.001$] to 184.49 [24.60] mg/dL at week 12 [$P < 0.001$]; mean [SD] percentage decrease, 32.97% [13.66%]). In group 2, no significant change from baseline was seen. In group 3, the decrease in TC level was significant at week 6 ($P < 0.001$), but no significant change was seen at week 12.

Figure 4 shows the mean TG levels by treatment group. In groups 1 and 2, the mean TG levels were similar to baseline at week 12. In group 3, the decrease was significant at week 6 ($P < 0.011$), but no change was seen at week 12. The mean (SD) percentage decrease over 12 weeks in group 3 was 34.11% (15.67%).

Serum Lp(a) levels are shown in **Figure 5**. At week 12, the mean Lp(a) levels were similar to baseline in all 3 groups.

The mean (SD) lipid tetrad index decreased in the following manner. In group 1, a statistically significant decrease in the lipid tetrad index was seen at week 6 (from 32,469.09 [29,316.5] to 16,952 [14,527.92]; $P = 0.04$), but no significant change was seen at week 12. In group 2, a statistically significant decrease was seen in 12 weeks (from 59,210.5 [34,309.2] to 30,070.3 [16,309.1] in the first 6 weeks

Figure 2. Mean (SD) high-density lipoprotein cholesterol (HDL-C) levels in Indian patients receiving treatment for dyslipidemia. *Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. †Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). ‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks. [§] $P < 0.05$ versus week 0.

Figure 3. Mean (SD) total cholesterol (TC) levels in Indian patients receiving treatment for dyslipidemia. *Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. †Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). ‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks. § $P < 0.05$ versus week 0.

[$P < 0.002$] to 16,329.5 [8946.2] in the next 6 weeks [$P < 0.003$]). In group 3, the decrease was significant at weeks 6 and 12 (from 46,521.1 [36,115.0] at baseline to 19,851.0 [15,185] at 6 weeks [$P < 0.005$] to 10,463 [4987] at 12 weeks [$P < 0.015$]).

Tolerability

Muscle pain (myalgia) developed in 5 (17%), 9 (30%), and 6 (20%) patients in groups 1, 2, and 3, respectively. Flushing was seen in 15 patients (50%) in group 2; this AE subsided within 3 weeks in all affected patients. All patients in group 3 tolerated the increase in niacin dose (ie, no flushing was seen). Dyspepsia was observed in 8 (27%) and 5 (17%) patients in groups 2 and 3, respectively. Elevated alanine aminotransferase levels were found at 12 weeks (but not at 6 weeks) in 2 (7%), 3 (10%), and 2 (7%) patients in groups 1, 2, and 3, respectively. These

patients were asked to discontinue treatment and maintain an optimal lipid profile by making lifestyle changes. None of the patients withdrew from the study.

DISCUSSION

CAD is a major health problem among people in India. Studies have shown that the prevalence of triple-vessel CAD is 45% in young Indians (age at onset, <40 years) compared with 8% to 15% in young people in Western countries.¹⁶⁻¹⁹

Genetic factors (eg, high Lp[a] levels) appear to play an important role in CAD, together with the conventional risk factors (eg, smoking, hypertension, hypercholesterolemia) and newly defined risk factors (eg, hypertriglyceridemia, high

Figure 4. Mean (SD) triglyceride (TG) levels in Indian patients receiving treatment for dyslipidemia. *Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. †Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). ‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks. [§] $P < 0.05$ versus week 0.

Figure 5. Mean (SD) lipoprotein (a) (Lp[a]) levels in Indian patients receiving treatment for dyslipidemia. *Group 1 received simvastatin monotherapy (20-mg tablet OD with meals) for 12 weeks. †Group 2 received niacin (sustained released [SR]) monotherapy (one 375-mg tablet taken with the evening meal for 1 week, followed by 500 mg OD with the evening meal for 1 week, and 500 mg BID with meals for 10 weeks). ‡Group 3 received simvastatin 10 mg and niacin (SR) tablets. The doses of niacin were 375 mg/d for 1 week and 500 mg/d for 11 weeks.

homocysteine levels, low HDL-C levels, insulin resistance). The conventional risk factors fail to explain the high incidence of CAD in Indians.

In Asian Indians, CAD is often premature (age at onset, <40 years), severe, and extensive, and follows a malignant course.⁷ Asian Indians have also shown a significantly higher prevalence of diabetes mellitus, hypertriglyceridemia, a low HDL-C level, and lower prevalences of cigarette smoking, systolic hypertension, and family history of CAD.⁷

The Indian patients in the present study had high TG and Lp(a) levels and low HDL-C levels. The mean baseline Lp(a) level was 36.18 (29.04) mg/dL. Many observational studies have reported that Indians have higher levels of Lp(a) compared with all other races except blacks.^{20–22} The Coronary Artery Disease

Among Indians study reported Lp(a) levels >30 mg/dL (the threshold at which the risk for CAD is believed to increase) in 25% of Asian Indians, 17% of whites, and 8% of Hispanics.²⁰ Among the 90 patients in the present study, 45 (50%) had Lp(a) levels >30 mg/dL. The mean TG level at the beginning of the trial was 220.84 (81.16) mg/dL. The mean baseline HDL-C level was 41.30 (5.52) mg/dL. Enas et al⁷ reported that HDL-C levels in Indian American men were 5 mg/dL lower than in European Americans and 15 mg/dL lower than in Japanese Americans. The mean LDL-C and TC levels in the present study were 175.32 (68.03) mg/dL and 261.28 (64.98) mg/dL, respectively. This TC level was higher than that reported in another population of Indian patients (199 mg/dL).²³ The higher values found here might have been due to the urban lifestyle of these patients (ie, many urban dwellers consume high-calorie diets and have sedentary lifestyles). The mean lipid tetrad index at the start of the study was 46,066.94 (34,600.39).

Apart from providing evidence concerning the typical pattern of dyslipidemia in Indians, this study also showed significant results for the efficacy of simvastatin and niacin alone or combined. We observed that simvastatin alone and in combination with niacin was associated with significant decreases in LDL-C and TC levels. Although the dose of simvastatin was lower (10 mg/dL) in combination therapy, the percentage decreases in LDL-C and TC levels were similar in monotherapy and combination therapy. Niacin monotherapy (1 g/d) was not associated with a change in LDL-C or TC level. A decrease of 20% to 30% in LDL-C levels has been reported with very high doses of niacin (4.5–6.0 g/d).² In the present study, the effect may have been smaller because of the low baseline levels of LDL-C and TC in group 2. Another explanation for the lower decrease in LDL-C in this group is beta-shift: 11 patients had increases in LDL-C.

The effects on other lipid levels varied according to treatment. Combination therapy was associated with a significant decrease in TG level at 6 weeks, whereas monotherapy with either drug was not associated with any change in TG level. In a study by Guyton et al,²⁴ a decrease of 16% to 29% was reported with niacin 1.5 to 2.0 g/d. The mean (SD) decrease of 20.44% (15.04%) with simvastatin was higher than that seen in other trials.^{25,26} One study, however, reported a dose-dependent reduction in TG level of 22% to 45% with all of the statins when the baseline levels were >250 mg/dL.²⁷

At 12 weeks, the mean increase in HDL-C level was significant with niacin monotherapy and with combination therapy. Few data are available concerning the effect of simvastatin on HDL-C. More studies are needed to ascertain the effect of statins on HDL-C.² Niacin monotherapy was most efficacious in lowering the Lp(a) levels, whereas simvastatin monotherapy and combination therapy were not associated with any changes in Lp(a) levels. At 12 weeks, niacin alone and in combination with simvastatin was associated with a significant decrease in the lipid tetrad index.

Niacin monotherapy was associated with more AEs (eg, flushing, myalgia, dyspepsia, elevated alanine aminotransferase level) compared with the other 2 treatments. Contrary to the typical assumption that the AEs increase when

lipid-altering agents are given in combination, this combination therapy was not associated with an increased prevalence of myalgia or elevated liver enzyme levels compared with either drug alone. The lower number of AEs found with combination therapy may have been due to the lower dose of both drugs in combination treatment.

Although this study showed the effects of simvastatin and niacin on the lipid profile, some important results could not be derived because of limitations of the study. Because the study was not randomized, the results in the 3 treatment groups cannot be compared. Because the patients in group 2 had lower levels of LDL-C and TC at baseline compared with the other 2 groups, the effect of niacin on high levels of these 2 parameters could not be observed. Better conclusions could be drawn from a study such as this if randomization were performed at the beginning.

CONCLUSIONS

In this population of Indian patients with dyslipidemia, simvastatin and niacin had beneficial effects on different parameters of the lipid profile. The simvastatin-niacin combination was associated with improvement in almost all of the parameters of the lipid profile. In this study population, the prevalence of AEs did not increase when low doses of simvastatin and niacin were combined.

REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
2. Mahley RW, Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001:971–1002.
3. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: Clues to mechanism of action of niacin. *Metabolism*. 1985;34:642–650.
4. Vega GL, Grundy SM. Lipoprotein responses to treatment with lovastatin, gemfibrozil, and nicotinic acid in normolipidemic patients with hypoalphalipoproteinemia. *Arch Intern Med*. 1994;154:73–82.
5. Martin-Jadraque R, Tato F, Mostazo JM, et al. Effectiveness of low-dose crystalline nicotinic acid in men with low high-density lipoprotein cholesterol levels. *Arch Intern Med*. 1996;156:1081–1088.
6. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med*. 1989;226:271–276.

7. Enas EA, Yusuf S, Mehta JL. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol.* 1992;70:945-949.
8. Enas EA, Mehta JL. Malignant atherosclerosis in young Indians. Thought on pathogenesis. Prevention and treatment. *Clin Cardiol.* 1995;18:131-135.
9. Sandholzer C, Halman DM, Sahe N, et al. Effect of apolipoprotein (a) polymorphism on the lipoprotein (a) concentration in seven ethnic groups. *Hum Genet.* 1991;86:607-614.
10. Allain CC, Poon LS, Chan CS, et al. Enzymatic determination of total serum cholesterol. *Clin Chem.* 1974;29:470-475.
11. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *J Lipid Res.* 1970;11:583-595.
12. Bucolo G, David H. Quantitative determination of serum triglycerides by use of enzymes. *Clin Chem.* 1973;19:476-482.
13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.
14. Metzmann E. Protein quantitation on both branches of the Heidelberger curve by monitoring the kinetic of immunoprecipitation. *Behring Inst Mitt.* 1985;78:167-175.
15. Enas EA, Garg A, Davidson MA, et al. Coronary heart disease and its risk factors in the first-generation immigrant Asian Indians to the United States of America. *Indian Heart J.* 1996;48:343-353.
16. Jalowiec DA, Hill JA. Myocardial infarction in the young and in women. *Cardiovasc Clin.* 1989;20:197-206.
17. Sharma SN, Kaul U, Sharma S, et al. Coronary arteriographic profile in young and old Indian patients with ischaemic heart disease: A comparative study. *Indian Heart J.* 1990;42:365-369.
18. Dave TH, Wasir HS, Prabhakaran D, et al. Profile of coronary artery disease in Indian women: Correlation of clinical, non invasive and coronary angiographic findings. *Indian Heart J.* 1991;43:25-29.
19. Negus BH, Willard JE, Glamann DB, et al. Coronary anatomy and prognosis of young, asymptomatic survivors of myocardial infarction. *Am J Med.* 1994;96:354-358.
20. Enas EA, Yusuf S, Garg A, et al. Lipoprotein (a) levels in Indian physicians. Comparison with black and white physicians in the U.S.A. *Indian Heart J.* 1994;46 (Suppl):185.
21. Enas EA, Yusuf S. Third meeting of the International Working Group on Coronary Artery Disease in South Asians. 29 March 1998, Atlanta, USA. *Indian Heart J.* 1999; 51:99-103.
22. Low PS, Heng CK, Saha N, Tay JS. Racial variation of cord plasma lipoprotein(a) levels in relation to coronary risk level: A study in three ethnic groups in Singapore. *Pediatr Res.* 1996;40:718-722.
23. Gopinath N, Chadha SL, Sehgal A, et al. What is 'desirable' lipid profile. *Indian Heart J.* 1994;46:325-327.
24. Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. *Arch Intern Med.* 2000;160:1177-1184.
25. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-1389.

26. Sweany AE, Shapiro DR, Tate AC, et al, for the NIDDM Study Group. Effects of simvastatin versus gemfibrozil on lipids and glucose control in patients with non-insulin-dependent diabetes mellitus. *Clin Ther.* 1995;17:186–203.
27. Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol.* 1998;81:66B–69B.

Address correspondence to: Dr. Kirandeep Kaur, Z15-A, Sewak Colony, Patalia 147001, Punjab, India. E-mail: kiransonhi@rediffmail.com, kiransondhi@hotmail.com