Efficacy and Safety of Chitosan HEP-40™ in the Management of Hypercholesterolemia: A Randomized, Multicenter, Placebo-controlled Trial

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Abstract

BACKGROUND: Hypercholesterolemia is an important risk factor for cardiovascular disease (CVD). OBJECTIVE: To compare the efficacy of a 12-week treatment regimen with HEP-40™ low-molecular weight chitosan given at daily doses of 1,200 mg, 1,600 mg, and 2,400 mg in reducing serum low-density lipoprotein cholesterol (LDL-C) in patients with low-to-moderate hypercholesterolemia. DESIGN: The study was a 16-week, multicenter, placebo-controlled, randomized study. Eligible patients were treatment-naive for lipid-lowering medications. Patients were randomly assigned to HEP-40 at the following doses: 400 mg three times daily, 800 mg twice daily, 800 mg three times daily, 2,400 mg once daily, or placebo for 12 weeks. The main outcome measure was the percent change in LDL-C after four weeks of treatment. RESULTS: Out of 283 patients screened, 105 (37.1%) fulfilled the inclusion criteria and 95 (90.4%) completed the study. The mean (SD) age was 53 (11) years and 62.3 percent were male. The majority of patients (82.9%) were at low 10-year risk for CVD. The results showed an overall treatment effect (p=0.040) with the highest difference from the placebo group observed for the HEP-40 2,400-mg once daily group (-16.9%, p=0.002), followed by 400 mg three times daily (-11.1%, p=0.054), 800 mg three times daily (-9.7%, p=0.065), and 800 mg twice daily (-8.7%, p=0.101). There were 29 predominantly mild adverse events reported by 24 (23%) patients related to the study treatment, most frequently constipation (3.0%) and diarrhea (3.0%). CONCLUSION: HEP-40 low-molecular weight chitosan, although not as effective as statins, is efficacious and safe in lowering LDL-C concentrations in treatment-naive patients with low-to-moderate hypercholesterolemia. (*Altern Med Rev* 2007;12(3):265-273)

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity, with the highest burden of illness in Western countries.[1] Increased risk for CVD has been directly associated with higher serum cholesterol concentrations and, more specifically, elevated low-density lipoprotein cholesterol (LDL-C).[2-7] Canada's National Cholesterol Education Program (NCEP) and 2006 Canadian guidelines for the management of dyslipidemia recommend HMG-CoA reductase inhibitors (statins) as the first-line pharmacological therapy for patients with hypercholesterolemia who do not respond to lifestyle modifications.[8,9] Although statins are effective in reducing LDL-C, it is estimated that 27-60 percent of patients do not achieve target LDL-C concentrations while on statin monotherapy.[10-12] Furthermore, known side effects of statins impair their use, particularly at higher doses.[13] Dietary supplements with low risk profiles could bridge this treatment gap.

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Chitosan is a natural compound produced commercially through the deacetylation of chitin, the structural element in the exoskeleton of crustaceans. Chitosan is believed to affect lipid concentrations by binding via its positively charged amino groups to negatively charged substrates in the gastrointestinal tract, such as fats and lipids, thus preventing absorption.[14-18] HEP-40™ (Enzymatic Polychitosamine Hydrolysate – 40 kDa; Diversified Natural Products; New York, NY) is a highly deacetylated (93%), low-molecular weight chitosan. HEP-40 is manufactured using enzymatic hydrolysis to digest chitosan into short-chain chitosans possessing a homogeneous molecular weight of approximately 40,000 Daltons. Preliminary studies have shown that chitosan is safe, well-tolerated, and effective in reducing total cholesterol (TC) and LDL-C.[15-18] These studies have been conducted using non-homogeneous patient samples that include healthy subjects[15-17] as well as those with significant comorbidities.[18]

The primary target population for treatment with low-molecular weight chitosan is otherwise healthy patients or those with controlled hypertension who have mild-to-moderate hypercholesterolemia. This placebo-controlled, randomized study evaluates the efficacy of HEP-40 low-molecular weight chitosan in reducing LDL-C in this patient population.

Objectives

The primary objective was to compare the efficacy of a four-week treatment regimen of HEP-40 at doses of 1,200 mg/day, 1,600 mg/day, and 2,400 mg/day, to placebo in reducing serum LDL-C in patients with low-to-moderate hypercholesterolemia; defined as LDL-C<154.4 mg/dL (4.0 mmol/L). The secondary objectives of the study compared the changes in LDL-C after eight and 12 weeks of study treatment for the four different HEP-40 dosing regimens to placebo, and the changes in serum concentrations of TC, HDL-C, and triglyceride (TG) concentrations at four, eight, and 12 weeks of treatment for the four HEP-40 dose regimens to placebo. Safety and tolerability of HEP-40 were also assessed.

Subjects and Methods

Subjects

Patients were recruited from the offices of 15 general practitioners and community specialists randomly selected across Canada. Inclusion criteria were: (1) ages 18-75 years; (2) at low (≤10%) or moderate (11-19%) 10-year risk for CVD according to the Framingham model;[19] (3) mild or moderate hypercholesterolemia, defined as LDL-C concentrations between 77.2 mg/dL (2.0 mmol/L) and 154.4 mg/dL (4.0 mmol/L); (4) treatment-naive for lipid-lowering medications; (5) stable diet and willing to continue on an NCEP Step 1 Diet[8] regimen for the duration of the study; and (6) women of child-bearing potential using an effective method of birth control for at least one month.

Exclusion criteria were: (1) presence of a condition or use of a medication that would render the patient unable to complete the study or produce significant risk to the patient, including diabetes, active renal disease (serum creatinine >2.0 mg/dL), known cardiac disease, HIV- or hepatitis B- or C-positive, allergy or intolerance to crustaceans and/or seafood products, pregnant or breastfeeding; (2) corticosteroid use; and (3) treatment with any investigational drug within 30 days of the screening visit.

Study Design and Treatment

This was a double-blind, multicenter, placebo-controlled, randomized study. Patient enrollment was conducted between February 6, 2006 and July 27, 2006, and patients were followed up until November 10, 2006. An independent ethics review board (IRB Services; Aurora, Ontario, Canada) and Health Canada's Natural Health Products Directorate approved the study. All patients gave written informed consent before entering the study. The trial was registered with ClinicalTrials.gov (Identifier: NCT00454831). The primary efficacy assessment was conducted at four weeks of treatment with follow-up assessments at eight and 12 weeks. During the screening visit patients were assessed for eligibility and underwent reviews of medical history and diet. Blood was drawn for lipid profile and safety parameter testing. For each patient, the 10-year risk for CVD was estimated using the Framingham model.[19]

During the baseline visit, if continued eligibility was confirmed, patients were randomized to one of the following five treatment groups:

- HEP-40 400 mg three times daily: treated with a total of 1,200 mg/day HEP-40, administered at breakfast (one capsule of 400 mg HEP-40), lunch (one capsule of 400 mg HEP-40), and dinner (one capsule of 400 mg HEP-40 and two capsules of 600 mg placebo).

- HEP-40 800 mg twice daily: treated with a total of 1,600 mg/day HEP-40, administered at breakfast (one capsule of 800 mg HEP-40), lunch (one capsule of 600 mg placebo), and dinner (one capsule of 800 mg HEP-40 and two capsules of 600 mg placebo).

- HEP-40 800 mg three times daily: treated with a total of 2,400 mg/day HEP-40, administered at breakfast (one capsule of 800 mg HEP-40), lunch (one capsule of 800 mg HEP-40), and dinner (one capsule of 800 mg HEP-40 and two capsules of 600 mg placebo).

- HEP-40 2,400 mg once daily: treated with a total of 2,400 mg/day HEP-40, administered at breakfast (one capsule of 600 mg placebo), lunch (one capsule of 600 mg placebo), and dinner (three capsules of 800 mg HEP-40).

- Placebo: treated with a total of 3,000 mg/day placebo, administered at breakfast (one capsule of 600 mg placebo), lunch (one capsule of 600 mg placebo), and dinner (three capsules of 600 mg placebo).

Five identical capsules per day were provided to all patients: one at breakfast, one at lunch, and three at dinner, regardless of the treatment group. HEP-40 was provided in capsules of 400 mg and 800 mg. Placebo capsules contained 600 mg microcrystalline cellulose.

Randomization

Randomization was performed using a permuted blocks randomization design. For each center, a series of permuted blocks of random size were generated. Each block included multiples of the five assignments, one for each group. Allocation was concealed from both subjects and the study personnel who enrolled participants by central control of the randomization sequence.

Outcome Measures

The primary efficacy outcome measure was the percent change in LDL-C between the baseline and four-week visits. Secondary outcome measures included the percent changes in LDL-C from baseline to eight and 12 weeks of treatment and the percent changes in TC, HDL-C, and TG from baseline to four, eight, and 12 weeks of treatment. Safety was assessed by the incidence of adverse events and clinically important changes in laboratory results, including serum 25-hydroxyvitamin D (25(OH)D). Safety assessments were performed at every follow-up visit and 30 days after the last dose of study medication. All laboratory tests were conducted at a central laboratory (LDS Diagnostic Laboratories; Pointe Claire, Quebec). Compliance with the protocol was ascertained by telephone contact between visits, dietary monitoring, and supplement accountability at follow-up visits.

Statistical Method

Descriptive statistics were produced for all variables, including patient demographic and baseline characteristics. One Way Analysis of Variance (ANOVA) was used to assess the statistical significance of the between-group differences with respect to the primary and secondary efficacy outcome measures. Planned pairwise contrasts based on the overall Linear Regression model were used to compare each HEP-40 treatment group to the placebo group. In addition, a planned contrast compared the HEP-40 combined group to the placebo group with respect to the percent change in LDL-C at four weeks of treatment. All planned contrasts were based on Tukey's test for Least Significant Difference (LSD). General linear models with repeated measures assessed between-group differences with respect to the rate of change in LDL-C over the 12-week treatment period.

The approach used for the statistical analysis of efficacy was according to the intent-to-treat principle. All patients who returned for at least one follow-up assessment were included in the efficacy analysis. Patients who did not return for follow-up assessment or were

withdrawn prior to randomization or prior to the four-week follow-up visit were not included in the efficacy analysis. There were no imputations or replacement of missing data, and all analyses were conducted on the observed cases. Patients who received at least one dose of study medication were included in the safety assessment. Serious and non-serious adverse events were described using the MedDRA dictionary of terms, version 9.0. The analyses were performed using SPSS version 12.0 for Windows.

Results

Patient Disposition

A total of 283 patients were screened and 178 were excluded for the following reasons: 66 (23.3%) did not fulfill the study criteria at screening and 102 (36%) had screening LDL-C above the study requirements. Eight (2.8%) did not fulfill the requirements for randomization at baseline and two (0.7%) withdrew at baseline. Of the remaining 105 eligible patients, 17 (16%) were randomized to 400 mg HEP-40 three times daily, 24 (23%) to 800 mg HEP-40 twice daily, 23 (22%) to 800 mg HEP-40 three times daily, 22 (21%) to 2,400 mg HEP-40 once daily, and 19 (18%) to the placebo group. Ultimately, 86 (82%) received HEP-40 treatment. Of the 105 study patients, 10 (9.5%) withdrew prior to the final 12-week assessment, of which nine were from the HEP-40 groups and one from the placebo group.

Baseline Characteristics

Table 1 describes the baseline characteristics and demographics of the patients. The mean (SD) age was 53 (11) years, with a range from 29-76 years; 62.3 percent were male. There were 87 (82.9%) patients at low (≤10%) risk and 18 (17.1%) patients at moderate (11-19%) 10-year risk for CVD according to the Framingham model. No significant between-group differences were found with respect to demographics and baseline characteristics and therefore no potential confounders were identified.

Descriptive Statistics

Lipid profile parameters for each HEP-40 treatment group and the placebo group at baseline, four, eight, and 12 weeks are summarized in Table 2. There were no significant between-group differences with respect to the absolute lipid parameters at baseline and follow up.

Table 1. Baseline and Demographic Characteristics of Patients

Characteristics:	Treatment Group						
	HEP-40					Placebo	Total
	400 mg TID	800 mg BID	800 mg TID	2400 mg QD	Combined		
N	17	24	23	22	86	19	105
Age							
Mean (SD)	55 (12)	53 (9)	52 (8)	51 (10)	52 (10)	53 (13)	53 (10)
Range	29-76	39-70	31-65	31-65	29-76	29-74	29-76
Gender, n (%)							
Female	5 (29.4)	6 (25.0)	5 (21.7)	9 (41.0)	25 (29.1)	9 (47.4)	34 (37.7)
Male	12 (70.6)	18 (75.0)	18 (78.3)	13 (59.1)	61 (70.9)	10 (52.6)	71 (62.3)
10-year coronary artery disease risk, n (%)							
Low (≤ 10%)	12 (70.6)	21 (87.5)	21 (91.3)	19 (86.4)	73 (84.9)	14 (73.7)	87 (82.9)
Moderate (11-19%)	5 (29.4)	3 (12.5)	2 (8.7)	3 (13.6)	13 (15.1)	5 (26.3)	18 (17.1)
Mean (SD) BMI (kg/m^2)	29.7 (4.1)	31.9 (11.3)	27.0 (3.7)	29.4 (4.6)	29.5 (7.0)	29.0 (4.8)	29.4 (6.6)
Hypertension: n (%)	1 (5.9)	1 (4.2)	2 (8.7)	2 (9.1)	5 (5.8)	2 (10.5)	7 (6.7)

Table 2. Lipid Profile by Treatment Group at Baseline, 4, 8, and 12 Weeks

Treatment group	Baseline		Week 4		Week 8		Week 12	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HEP-40 400 mg TID	N = 17		N = 14		N = 13		N = 13	
LDL-C (mg/dL)	149.5	20.4	145.1	18.5	143.0	14.5	146.4	26.8
Total Cholesterol (mg/dL)	218.2	25.9	218.2	20.9	210.7	23.8	224.0	22.1
Triglycerides (mg/dL)	128.2	58.8	144.4	95.6	157.0	112.1	178.6	194.4
HDL-C (mg/dL)	43.4	15.5	44.4	11.3	43.2	17.6	43.8	14.4
HEP-40 800 mg BID	N = 24		N = 23		N = 23		N = 23	
LDL-C (mg/dL)	143.6	36.8	138.4	35.8	134.5	33.3	143.4	31.8
Total Cholesterol (mg/dL)	216.0	38.5	210.9	42.8	209.2	35.1	211.6	34.3
Triglycerides (mg/dL)	171.3	128.6	170.4	111.3	172.7	157.8	155.2	86.2
HDL-C (mg/dL)	38.4	11.1	37.2	7.7	38.5	7.4	37.3	7.5
HEP-40 800 mg TID	N = 23		N = 22		N = 22		N = 21	
LDL-C (mg/dL)	138.4	28.4	137.0	30.3	132.5	30.9	134.2	37.1
Total Cholesterol (mg/dL)	204.6	30.8	207.1	28.8	206.0	29.4	209.2	35.7
Triglycerides (mg/dL)	127.5	90.8	135.2	123.1	142.3	109.0	147.6	163.4
HDL-C (mg/dL)	46.8	16.9	48.6	16.3	47.3	14.9	44.3	13.7
HEP-40 2400 mg QD	N = 22		N = 20		N = 20		N = 20	
LDL-C (mg/dL)	146.1	17.4	130.7	20.1	132.3	21.2	143.6	21.2
Total Cholesterol (mg/dL)	210.7	20.5	200.1	26.5	201.2	22.5	208.3	23.8
Triglycerides (mg/dL)	144.9	99.1	159.5	85.0	157.2	77.2	132.6	62.0
HDL-C (mg/dL)	39.0	12.9	38.4	10.4	38.3	11.6	38.5	11.9
HEP-40 Combined	N = 86		N = 79		N = 78		N = 77	
LDL-C (mg/dL)	144.0	27.3	137.3	27.7	134.9	27.1	141.5	30.0
Total Cholesterol (mg/dL)	212.0	30.1	208.5	31.7	206.6	28.5	212.3	30.4
Triglycerides (mg/dL)	144.3	100.1	152.7	105.2	157.7	118.4	151.6	128.9
HDL-C (mg/dL)	41.8	14.3	42.1	12.7	41.7	13.2	40.6	12.0
Placebo	N = 19		N = 18		N = 18		N = 18	
LDL-C (mg/dL)	139.5	34.5	149.0	26.5	148.6	29.5	149.1	26.4
Total Cholesterol (mg/dL)	206.5	31.0	225.3	37.1	225.2	45.6	219.7	34.0
Triglycerides (mg/dL)	131.1	82.5	159.2	110.0	162.7	139.3	147.2	72.7
HDL-C (mg/dL)	43.2	11.9	46.9	14.4	43.5	13.4	41.5	14.4

SI conversion: to convert LDL-C, HDL-C, or total cholesterol to mmol/L, multiply by 0.0259; To convert triglycerides to mmol/L, multiply by 0.0113.

Primary Efficacy Analysis

Table 3 summarizes the percent change from baseline to follow-up visits for all lipid profile parameters. With respect to the primary outcome measure, the percent change in LDL-C after four weeks of study treatment, the ANOVA results showed a significant treatment effect (p=0.040). The ANOVA planned comparisons showed the highest difference in percent change in LDL-C from the placebo group was observed for the 2,400-mg once daily group (-16.9%; p=0.002).

Table 3. Percent Change in Lipid Parameters by Treatment Group

Week	Lipid Parameter	Percent Change from Baseline										P value[1]	HEP-40 group versus Placebo			
		Treatment Group											Mean (SE) Difference in Percent Change (P Value[2])			
		HEP-40 400 mg TID		HEP-40 800 mg BID		HEP-40 800 mg TID		HEP-40 2400 mg QD		Placebo			HEP-40 400 mg TID	HEP-40 800 mg BID	HEP-40 800 mg TID	HEP-40 2400 mg QD
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD					
4	LDL-C (mg/dL)	-3.9	12.7	-1.5	16.6	-2.5	15.2	-9.8	13.5	7.2	18.6	0.040	-11.1 (3.9) (0.054)	- 8.7 (5.2) (0.101)	-9.7 (5.2) (0.065)	-16.9 (5.2) (0.002)
	TC (mg/dL)	-1.1	10.3	-3.1	7.8	2.2	14.1	-5.0	7.4	7.3	12.0	0.008	-8.4 (3.8) (0.032)	-10.4 (3.5) (0.004)	-5.1 (3.5) (0.141)	-12.3 (3.6) (0.001)
	TG (mg/dL)	11.5	44.3	8.6	66.5	7.8	33.6	21.4	68.1	18.1	40.7	0.904	-6.5 (19.1) (0.733)	-9.5 (17.5) (0.587)	-10.3 (17.3) (0.553)	3.3 (17.8) (0.853)
	HDL-C (mg/dL)	4.8	17.9	4.0	13.9	6.4	22.9	0.9	11.3	9.4	15.7	0.654	-4.6 (6.1) (0.455)	-5.4 (5.6) (0.338)	-3.0 (5.5) (0.588)	-8.5 (5.7) (0.140)
8	LDL-C (mg/dL)	-7.2	13.0	-7.2	15.3	-5.6	13.7	-9.7	15.5	8.0	13.8	0.006	-15.1 (5.4) (0.006)	-15.1 (4.7) (0.002)	-13.5 (4.8) (0.006)	-17.7 (4.9) (0.001)
	TC (mg/dL)	-5.6	15.9	-3.5	8.3	-0.3	9.0	-4.5	11.5	9.5	15.0	0.002	-15.1 (4.2) (0.001)	-13.0 (3.8) (0.001)	-9.9 (3.8) (0.012)	-14.0 (3.9) (0.001)
	TG (mg/dL)	13.9	43.9	0.2	47.3	15.2	42.3	24.9	58.2	30.2	56.1	0.372	-16.3 (18.0) (0.367)	-29.9 (15.9) (0.064)	-14.9 (16.3) (0.360)	-5.3 (16.6) (0.751)
	HDL-C (mg/dL)	-3.4	15.2	5.7	10.4	4.4	16.2	-0.1	15.9	4.1	17.7	0.376	-7.5 (5.4) (0.171)	1.7 (4.8) (0.730)	0.3 (4.9) (0.956)	-4.1 (5.0) (0.412)
12	LDL-C (mg/dL)	-4.9	19.3	-0.1	17.0	-2.7	17.3	-2.6	15.0	8.4	18.8	0.196	-13.3 (6.3) (0.38)	-8.4 (5.5) (0.126)	-11.0 (5.6) (0.050)	-10.9 (5.6) (0.055)
	TC (mg/dL)	-0.4	10.5	-2.2	9.9	1.0	11.1	-1.5	9.8	5.7	9.0	0.123	-6.2 (3.6) (0.090)	-7.9 (3.2) (0.014)	-4.7 (3.3) (0.151)	-7.2 (3.3) (0.030)
	TG (mg/dL)	16.0	69.5	-2.2	32.8	9.3	38.2	3.6	37.3	24.9	49.0	0.367	-8.9 (16.0) (0.579)	-27.2 (14.1) (0.057)	-15.7 (14.0) (0.280)	-21.4 (14.6) (0.146)
	HDL-C (mg/dL)	-0.8	12.6	2.6	13.9	-2.8	10.2	0.8	13.1	-4.1	15.5	0.492	3.3 (4.7) (0.489)	6.7 (4.1) (0.111)	1.3 (4.3) (0.758)	4.9 (4.3) (0.250)

TC = Total Cholesterol; TG = Triglycerides;
[1] P value based on ANOVA; [2] P value based on Linear Regression Analysis and Post-Hoc Tukey's test for Least Significant Difference (LSD)

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Secondary Efficacy Analysis

A significant overall treatment effect was observed at four weeks with respect to the percent change in TC (p=0.008). The ANOVA planned contrasts showed the mean difference in percent change of TC from the placebo group was -12.3 percent (p=0.001) for the 2,400-mg once daily group, -10.4 percent (p=0.004) for the 800-mg twice daily group, and -8.4 percent (p=0.032) for the 400-mg three times daily group.

After eight weeks of treatment, a significant overall treatment effect was observed in the percent changes in LDL-C (p=0.06) and TC (p=0.002). Planned ANOVA contrasts for the percent changes in LDL-C and TC at eight weeks showed significantly higher decreases in all HEP-40 groups compared to placebo, with the highest difference observed for the HEP-40 2,400-mg once daily group.

After 12 weeks, no significant overall treatment effects were observed with respect to the change in lipid profile parameters. The results of the planned contrasts showed a significant difference from placebo for the groups taking HEP-40 800 mg twice daily or 2,400 mg once daily with respect to the percent change in TC (-7.9%; p=0.014 and -7.2%; p=0.030, respectively).

Safety

Twenty-nine non-serious adverse events (NSAEs) were reported by 24 (23%) patients. The overall incidence of NSAEs was similar among the study groups. The majority (72.4%) of the treatment-emergent NSAEs were mild in intensity, the most frequently reported being constipation (3.0%) and nausea (3.0%). No serious adverse events attributed to the study treatments nor clinically important changes in any laboratory safety parameters were reported. Serum 25(OH)D concentrations were tested at baseline and final assessment. After 12 weeks, the mean changes in 25(OH)D were +3.29 ng/mL for patients treated with HEP-40 and +4.97 ng/mL for placebo-treated patients (p=0.472).

Discussion

This study showed HEP-40 low-molecular weight chitosan is efficacious in reducing serum LDL-C and is safe and well-tolerated. A dose-response relationship was demonstrated with higher and more concentrated doses of HEP-40 producing greater reductions in LDL-C. Significant reductions in TC were also observed at four weeks and eight weeks, with a trend toward significance at 12 weeks.

Efficacy results and safety data are in agreement with those reported in the literature and provide further evidence in support of the lipid-lowering benefits of chitosan,[15-18] and more specifically the safety and efficacy of low-molecular weight chitosan. Furthermore, concerns that chitosan can limit serum vitamin D absorption[20] were not supported by the current study.

The results should be interpreted in the context of hypercholesterolemia and the importance of early and safe treatment for the prevention of disease progression. All patients had low or moderate risk for CVD and were treatment-naive; therefore, early treatment with lifestyle modifications prior to initiating treatments with pharmacological agents, including statins, would be indicated for these patients.[9] The aim of lipid management treatment in these patients should also include preventing further increases in LDL-C. In the placebo group, LDL-C and TC increased, showing the natural progression of disease. It is reasonable to assume that, in the future, these patients might require pharmacological treatment due to increases in LDL-C concentrations beyond the recommended targets for their respective CVD risk group. On the other hand, HEP-40 patients experienced a reduction in LDL-C and TC, indicating a slower disease progression and reduced lipid burden. For these patients, prescriptive pharmacological treatment could be avoided or delayed. In consideration of the increasing concern regarding adverse effects of lipid-lowering pharmaceuticals, this observation of a potential statin-sparing effect has important implications for the initial clinical management of this patient population.

Potential limitations of the current study include the risk for unblinding when treating physicians and patients were informed of their laboratory results at the four-week visit. Although this may have affected the results at eight and 12 weeks, the bias would not have affected the primary efficacy outcome measure of

change in LDL-C after four weeks. Another limitation might be the restriction of the study to treatment-naive patients. As a result, we are not able to assess the competitive or synergistic effect of HEP-40 with other lipid-lowering treatments, including statins or fibrates. However, this exclusion is compatible with the general aim of the current study: to assess the effectiveness of HEP-40 in newly diagnosed patients with hypercholesterolemia who are treatment-naive. The study design provided data on the non-confounded, independent, lipid-lowering effect of HEP-40 in this population. The magnitude of the effect on LDL-C reduction observed with HEP-40 of approximately 11 percent is lower when compared to that observed with statins;[4-8] however, this effect is higher than that observed with other non-prescription products.[21-28]

The strengths of the current study include the prospective, blinded, and randomized design. By including different dosing regimens of HEP-40, the results demonstrate a dose-response relationship providing evidence of a beneficial effect. Patients were recruited from randomly selected family physician and community specialist practices, thus allowing generalization of the results to the target population. The use of a central laboratory, minimizing measurement errors and variations, represents another strength of the study.

Conclusion

The results of this randomized, double-blind, placebo-controlled trial show HEP-40 low-molecular weigh chitosan is efficacious and safe in lowering serum LDL-C concentrations in treatment-naive patients with mild-to-moderate hypercholesterolemia, although not as effective as a statin drug. The study results support the use of a concentrated, single daily dose of 2,400 mg/day HEP-40 as being most effective after four weeks of treatment. This study has implication for the management of patients with mild-to-moderate hypercholesterolemia for whom treatment with a statin is either not indicated or tolerated.

Disclosures

An independent statistical analysis was performed by John Sampalis, PhD, of McGill University and JSS Medical Research, Inc. JSS Medical Research, Inc. was paid by Diversified Natural Products to conduct this study. Shahin Jaffer, MD, was paid as a consultant and received grants for patient recruitment. All investigators received grants for patient recruitment.

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