

Research Article



A Comparison of the Long-Term (1 year) Lipid Modifying Effects of D-003 (Sugarcane Wax Acids) and Policosanol: A Randomized, Double-Blind Study.

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ABSTRACT

The main goal of dyslipidemia management is to lower serum low-density lipoprotein-cholesterol (LDL-C). D-003 is a mixture of sugarcane wax acids with cholesterol-lowering and bone protective effects. Policosanol, a mixture of higher aliphatic alcohols purified from the same source, is a cholesterol-lowering agent. D-003 administered for short-term (8 weeks) was more effective than policosanol (both at 5 and 10 mg/day) for lowering LDL-C, total cholesterol (TC), and for increasing high-density lipoprotein-cholesterol (HDL-C). To compare the long-term (1 year) efficacy, safety and tolerability of D-003 and policosanol (titrated from 5 to 20 mg/day) in hypercholesterolemic patients. After a 5-week baseline period, 165 patients were double-blind randomized to D-003 or policosanol 5 mg/day for 3 months. The dose was doubled in subjects with LDL-C reductions \leq 15% and the same was repeated at 6 months. LDL-C reduction was the main efficacy outcome. Data were analyzed according to Intention to Treat. D-003 and policosanol (5 mg/day for 3 months) reduced ($p < 0.0001$) similarly LDL-C by 19.7% and 19.6%, respectively. These effects did not wear off, even enhanced, with long-term treatment and dose increases. At study completion D-003 reduced LDL-C (34.3%, $p < 0.0001$ versus baseline) more ($p < 0.05$) than policosanol (30.0%). The frequency of dose titration with policosanol (66/83, 79.5%) was higher ($p < 0.01$) than with D-003 (47/82, 57.3%). The mean estimated doses (mg/day) at 12 months were 10.2 (D-003) and 13.9 (policosanol). The frequency of LDL-C reductions \geq 15% with D-003 (72/82, 87.8%) was higher ($p < 0.01$) than with policosanol (66/82, 79.5%). D-003 and policosanol decreased ($p < 0.0001$) TC (21.7% and 19.5%, respectively) and increased HDL-C (12.0% and 7.4%, respectively), D-003 being more effective for increasing HDL-C ($p < 0.01$). D-003 reduced LDL-C/HDL-C and TC/HDL-C ratios ($p < 0.0001$) to 38.8% and 27.7%, respectively, and policosanol to 30.0% and 20.4%, respectively. D-003 was the most effective for lowering both ratios ($p < 0.05$). Treatments unchanged triglycerides. Both treatments were safe and well tolerated. Long-term administration (1 year) of D-003 (mean dose 10.2 mg/day) persistently exhibited long-term cholesterol-lowering efficacy, and was more effective than policosanol (mean dose 13.9 mg/day) for lowering LDL-C, both ratios, and for increasing HDL-C. Both treatments were safe and well tolerated.

Keywords: D-003, sugarcane wax acids, lipid modifying, policosanol, hypercholesterolemia, long-term

INTRODUCTION

Hypercholesterolemia (HC) is one of the major risk factors for atherosclerotic vascular disease, whose atherothrombotic complications lead elevated morbidity and mortality worldwide.^{1,2} Thus, HC prevention and management is a crucial issue for coronary prevention in the main consensus guidelines, such as the European guidelines for dyslipidemia management (2011) and cardiovascular prevention (2012)^{3,4} and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, updated in late 2013.⁵

These guidelines agree in many respects, but differ on important points, such as the drastic change in the approach to the starting of lipid-lowering therapy and the therapeutic targets. Despite their differences, the European and new ACC/AHA guidelines underline elevated serum low-density lipoprotein (LDL-C) levels as a major cardiovascular risk factor and the relevance of LDL-C reduction for coronary prevention. While adherence to a therapeutic lifestyle, including a low-fat, low-cholesterol diet, is recognized as the masterpiece of HC management and coronary prevention in both guidelines, this alone

often is not enough to bringing LDL-C to desired targets.³⁻⁵ Pharmacotherapy must be then indicated, mainly in high risk subjects.⁷⁻¹¹

Despite cholesterol-drugs are safe, they induce drug-related adverse experiences (AE), mainly liver and skeletal muscle function disturbances.^{10,11} Drug safety is a pivotal matter for cholesterol-lowering therapy because they should be given for long-term. Searching for safer treatments, therefore, some plant-derived cholesterol-lowering products have been investigated.

Policosanol is a mixture of 8 high molecular weight alcohols purified from sugarcane wax that contains octacosanol as the main component with cholesterol-lowering effects demonstrated in experimental and clinical studies,¹²⁻²² despite some negative studies.^{23,24} Policosanol lowers cholesterol by inhibiting cholesterol biosynthesis, regulating HMGCoA reductase activity through the activation of AMP kinase activity.²⁵⁻²⁸

Also, policosanol increases the LDL receptor-dependent processing and the clearance of ¹²⁵I-labeled LDL-C administered to rabbits with HC induced with a cholesterol-free, casein-rich diet.¹³ Also, policosanol



exhibits pleiotropic effects, such the reduction of the susceptibility of LDL to undergo lipid peroxidation.²⁹⁻³¹

D-003 is a mixture of 13 higher aliphatic acids isolated also from sugar cane wax whose main component is octacosanoic acid. D-003 has been shown cholesterol-lowering effects in experimental and clinical studies.³²⁻⁴³

D-003 inhibits cholesterol synthesis prior to mevalonate formation by regulating HMGCoA reductase activity.⁴⁴ D-003 also inhibits lipid peroxidation and protein oxidation, its antioxidant effects being superior as compared to those of policosanol.^{36,37, 45-47} Also, D-003 has been shown bone protective effects in experimental and clinical studies.^{41-43, 48-50}

A short-term (8 weeks) comparative study demonstrated that D-003 (5 and 10 mg/day) was more effective than policosanol (5 and 10 mg/day) for lowering serum LDL-C, total cholesterol (TC), and for increasing high-density lipoprotein-cholesterol (HDL-C) in hypercholesterolemic subjects.³⁹ No previous study, however, has compared the long-term effects of both treatments.

In light of these issues, this study compared the long-term (1 year) efficacy, safety and tolerability of D-003 and policosanol administered from 5 to 20 mg/day to hypercholesterolemic patients.

PARTICIPANTS AND METHODS

Study Design

This randomized, double-blinded, parallel-group, comparative study was conducted at the Medical Surgical Research Centre (Havana, Cuba). Study protocol was approved by the Institutional Review Committee and later on by the Cuban Centre for State Drug Control, as regulates Cuban Good Clinical Practices (GCP) guidelines. This study was audited for the Cuban Centre for State Drug Control, adherence to GCP being confirmed.

At enrolment, study participants provided voluntary and free written informed consent (*visit 1*).

Men and women with serum TC ≥ 5.2 mmol/L, aged 20 to 75 years, were enrolled in the study and entered in a diet-only baseline period. Subjects were instructed to follow a diet based on a daily cholesterol intake < 300 mg, total fats $\leq 30\%$ of total calories, with < 10% of total calories from saturated fats, 10% from polyunsaturated, and 10% to 15% from monounsaturated fats.

After concluding the 5-week diet-only period, serum lipid profile tests were performed twice within 15 days (weeks 4 and 5 of baseline period). Baseline lipid profile values were the mean of the two successive determinations.

When blood samples for the second testing were drawn, aliquots were taken for determining blood safety indicators, including haematological (hemoglobin, hematocrit, platelet counts) and blood biochemical (alanine aminotransferase –ALT-, aspartate aminotransferase –AST-, creatinphosphokinase –CPK-, fasting glucose and creatinine) indicators.

Eligible patients were randomized, under double-blind conditions, to policosanol or D-003 (both at 5 mg/day) for the first 3 months (*Visit 2*). Subjects attended to visits at 3, 6, 9 and 12 months on therapy (*visits 3 – 6*). Once concluded the first 3 months, the dose was doubled in patients with LDL-C reductions $\leq 15\%$, and the same was repeated at 6 months. The highest dose was 20 mg/day. The total duration of the active treatment was 12 months. Subjects attended to follow-up visits every 3 months (*Visits 3 – 6*). Physical examination was performed at each visit. Treatment compliance and AE were controlled from visits 3 to 5. Laboratory analyses were performed at baseline and every 3 months.

Dosage and Administration

At visit 2, eligible patients were assigned to receive identical policosanol or D-003 5-mg tablets according to a computer-generated randomization code using balanced blocks and 1/1 allocation ratio. Patients allocated to receive D-003 or policosanol consumed daily one D-003 or policosanol 5 mg-tablet + one matched placebo tablet (double-dummy). According to their progressive inclusion in the trial, patients received study treatments in identical coded packages, being instructed to take them once a day with the evening meal for the first 3 months. Dose titration was conducted at months 3 and 6 on therapy, for which subjects should take the double quantity of tablets in the next period up to take 4 tablets a day. So, the highest dose to be taken by D-003 treated subjects was 20 mg/day, since this is the dose of policosanol that reach the ceiling LDL-C decrease. Subjects titrated to such dose remained on there for the next step.

Study Participants

Inclusion Criteria

Enrolled patients were eligible for randomization if they had the following values (mmol/L) at the end of the diet-only period: LDL-C ≥ 3.4 ; TC ≥ 5.2 . Triglycerides were restricted to be <4.52 to can calculate LDL-C values as per the Friedewald equation.⁵¹

Exclusion Criteria

Patients were excluded if they had active hepatic or renal diseases, diagnosed neoplastic diseases, uncontrolled hypertension (diastolic blood pressure ≥ 100 mm Hg), uncontrolled diabetes mellitus and the following baseline laboratory values: glucose > 7 mmol/L; creatinine > 130 $\mu\text{mol/L}$; alanine amino transferase (ALT) or aspartate amino transferase (AST) > 55 mmol/L. Patients who had had any serious event leading to hospitalisation within the 6 months prior to study, as well as pregnant, lactating or women of childbearing potential without contraceptive protection were also excluded from the trial.

Withdrawals

Causes for study withdrawals, as defined in the protocol, included the occurrence of AE justifying such decision by physician or patients' perception; unwillingness to follow-



up, and major protocol violations, such as consumption of any other lipid-lowering therapy different from study treatments, and no consumption of study medication for ≥ 15 consecutive days

Compliance Assessment

Compliance with study treatments was considered good if patients had consumed at least 90 % of the scheduled tablets since the previous visit, documented by counts of remainder tablets, interviews and control charts. Compliance with diet was assessed by interview and body weight control.

Concomitant Medications

Consumption of drugs or supplements affecting the lipid profile other than study treatments was forbidden from the enrolment up to the end of the study.

Efficacy variables

Reduction of serum LDL-C levels was the main efficacy outcome. Treatments were considered effective only if at study completion they lowered LDL-C by at least 15 % as compared with baseline. D-003 was considered more effective than policosanol if produced a LDL-C reduction significantly higher than that reached with policosanol. Also, the frequency of patients reaching reductions $\geq 15\%$ compared with baseline was analysed. Other lipid profile variables (TC, HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, triglycerides) were secondary outcomes.

Safety and Tolerability

Safety and tolerability were assessed through data obtained from physical examination, laboratory tests and interviews for AE. According to their intensity, AE were classified as mild, moderate or serious.

Mild AE being those AE that did not require stopping of study medication nor specific treatment of AE; moderate AE those requiring withdrawal of study medication and/or treatment of AE, and serious AE those fatal (leading to death) and those non-fatal, but leading to, or prolonging hospitalizations.

In addition, AE were ascertained according to their causal relation with the treatments as definitively, probably, possibly or doubtful by using the Naranjo algorithm.⁵²

Laboratory Analysis

Venous blood samples were collected after 8-10 hours overnight fast. Serum TC and TG were determined through enzymatic methods with reagent kits from Randox (UK) whereas HDL-C was determined as the cholesterol content in the supernatant obtained after β -lipoproteins precipitation.⁵³ LDL-C values were calculated with the Friedewald equation.⁵¹

The analyses of blood biochemistry safety indicators were done by using reagent kits from the same supplier, in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the laboratory of the Medical Surgical Research Centre.

A systematic quality control was performed throughout the trial. Precision of the methods was determined according to the within (r) and between-day (R) data variations, and the accuracy assessed by comparisons with reference standards. The coefficients of variations (CV) (%) for TC were $r = 2.4$; $R=2.7$; for triglycerides $r = 3.6$, $R = 3.9$, for HDL-C $r = 3.2$; $R = 3.7$. The differences against the standard references were $< 4\%$ for TC and $< 5\%$ for triglycerides. The assay bias was maintained throughout the study.

Haematological indicators were determined by standard laboratory methods conducted in the automatic equipment Haematological Complex located at the same laboratory.

Statistical Analysis

All analyses were performed by Intention-to-Treat, meaning patients who withdrew from the trial were included in all analysis, disregarding the degree of compliance with treatment.

For the primary efficacy variable we assumed that D-003 would show a difference in serum LDL-C reduction of at least 5% compared with policosanol. For that, and based in a 80 % test power and 5% of significance level, a sample size of 150 patients (75 per group) would be enough (MedCalc, 2000; SAS/STAT). Allowing for an estimated dropout rate of 10 %, recruitment of at least 165 patients was needed.

Baseline values were defined as the mean values of lipid profile values obtained in the two consecutive determinations performed at the end of the diet-only period. Continuous data were analyzed with the Wilcoxon test for paired samples (within group comparisons) and with the Mann Whitney U test (between group comparisons). Comparisons of categorical data were made using the Fisher's Exact Probability Test. All statistical tests were two-tailed, with significance taken at $\alpha = 0.05$. Statistical analyses were performed using the statistical package program Statistics for Windows (Release 4.2; Copyright StatSoft, Inc. US) and SAS/STAT statistical package (Release 8.2 for Windows).

RESULTS

Baseline Characteristics and Study Withdrawals

Of the 180 patients enrolled, 165 (137 women, 28 men) were randomized to active treatment (visit 2), all of which concluded the study. Fifteen (15) enrolled patients were not randomized due to the following reasons: serum LDL-C < 5.2 mmol/l (4 subjects), TC < 3.4 mmol/l (3) and TG > 4.52 mmol/l (4) at the end of the diet-only period; glucose > 7.0 mmol/l (2 participants) and systolic pressure > 160 mmHg (2).

Baseline characteristics were similar in both study groups (Table 1). Despite the study was not conducted specifically in older subjects, the mean age of study population was 63 years. Gender distribution shows that



included women (137/165, 83.0 %) outnumbered men (28/165, 17.0 %), this condition being also statistically similar in the two groups. Study population had some other concomitant risk factors beyond hypercholesterolemia, all balanced in both groups, the most frequent (>50.0%) being women older than 55 years (70.3%) and documented hypertension (62.4%). In addition, a relatively high frequency (> 15%) of obesity ($\text{kg/m}^2 \geq 30$) (15.2%), coronary heart disease (CHD) (13.9%), men older than 45 years (15.8%) and diabetes (17.6%) was seen among the randomized subjects.

Family history of premature CHD was also highly frequent (35.8%), meanwhile the frequency of smokers was relatively low (10.3%).

The frequency of concomitant therapy was high (78.2%) and well matched in both groups. Antihypertensive drugs (diuretics, angiotensin converting enzyme inhibitors – ACEI) and β -blockers were the most common medications consumed by study subjects.

Of the 165 randomized participants, 160 (97.0%) concluded the study, and only 5 (3.0%) (3 policosanol, 2 D-003) were premature withdrawals. Of them, the two D-003-withdrawals were due to unwillingness to follow-up (1) and suffering an AE (a hip fracture caused by a car accident at 11.5 months on treatment)(1). The three policosanol cases who withdrew from the study were due to unwillingness to follow-up (2) and address changes that prevented attend to the visits (1).

Efficacy Analysis

Compliance with study treatments was good since 150/165 (90.9 %) of the patients (76 in D-003, 74 in policosanol group) reached the criterion of good compliance defined in the study protocol. Compliance with diet was good, not optimal, as revealed patient declarations, this situation being similar for both groups.

Effects on Lipid Profile

Table 2 lists the effects on lipid profile. Both groups showed similar lipid profile values at baseline. D-003 and policosanol (5 mg/day for 3 months) reduced significantly ($p < 0.0001$).

Similarly LDL-C, the main study outcome, by 19.7% and 19.6%, respectively. These effects did not wear off, even enhanced, with long-term treatment and dose increases.

At study completion D-003 reduced LDL-C (34.3%, $p < 0.0001$ versus baseline) more ($p < 0.05$) than policosanol (30.0%). The frequency of LDL-C reductions $\geq 15\%$ with D-003 (72/82, 87.8%) was higher ($p < 0.01$) than with policosanol (66/83, 79.5%).

According to the reductions of LDL-C values, the frequency of dose titration in policosanol (66/83, 79.5%) was higher ($p < 0.01$) than in D-003 (47/82, 57.3%) group.

The mean estimated doses (mg/day) after 12 months on treatment were 10.2 (D-003) and 13.9 (policosanol).

Oral administration of D-003 and policosanol decreased significantly TC from the first interim control, and such decreases were not only persistent, but enhanced, after 12 months on therapy, when they achieved mean reductions of 21.7% (D-003) and 19.5% (policosanol) ($p < 0.0001$ versus baseline, no differences between both groups). In addition, after 3 months on therapy, both D-003 and policosanol at 5 mg/day were effective for increasing significantly HDL-C ($p < 0.0001$ versus baseline for both comparisons), an effect also persistent throughout the study that reached final increases of 12.0% with D-003 and 7.4% with policosanol. D-003 was more effective than policosanol for increasing HDL-C ($p < 0.01$). Treatments failed to modify TG values.

Oral treatment with D-003 (5 – 20 mg/day) also reduced LDL-C/HDL-C ratio ($p < 0.0001$) by 27.9% and 38.8%, after 3 and 12 months on treatment, respectively, and the TC/HDL-C ratio ($p < 0.0001$) by 22.1% and 27.9%, respectively.

In turn, policosanol decreased significantly LDL-C/HDL-C and TC/HDL-C ratios ($p < 0.0001$ for all comparisons) by 20.8% and 26.3%, respectively (at 3 months) and by 20.4% and 30.0%, respectively (at 12 months). D-003 was more effective than policosanol for lowering both ratios ($p < 0.05$).

As a whole, D-003 (5 – 20 mg/day) was more effective than policosanol for lowering LDL-C and both ratios, as well as for increasing HDL-C. The effects on lipid profile induced with both drugs were significant respect to baseline from the interim check-up, but the differences between treatments at such time were not significant.

Safety Profile and Tolerability

Both treatments were safe and well tolerated.

Consumption of D-003 or policosanol did not impair significantly any of the physical and laboratory (haematology, blood biochemistry) indicators (Data not shown for simplicity).

As stated, 5 patients (2 D-003, 3 policosanol) withdrew from the study, but only 1 (D-003-treated) was due to an AE, consisting in a hip fracture after a car accident. Overall, 11 subjects (7 from policosanol, 4 from D-003 group) referred to have experienced 12 AE during the study.

Four subjects treated with D-003 reported hip fracture after big trauma as referred above (1 withdrawal), pneumonia (1), heartburn (1) and sacrolumbalgia (1); while the five subjects from the policosanol group experienced insomnia (2), dizziness (1), somnolence (1), gastric ulcer (1), pyelonephritis (1) and dengue (1). Exception the hip fracture (1 D-003) and dengue (1 policosanol), both considered as not treatment-related, the other

AE were at least possibly treatment-related according to causality link with the treatment.



Table 1: Baseline characteristics of study population

Characteristics	Policosanol (n = 83)		D-003 (n = 82)	
Age (years) (X ± SD)	63.5 ± 7.4		62.6 ± 7.4	
Bodyweight/mass index (kg/m ²) (X±SD)	26.18 ± 4.59		26.12 ± 3.98	
Women, n (%)	70 (84.3%)		67 (81.7%)	
Men, n (%)	13 (15.7%)		15 (18.3%)	
Personal history				
	n	%	n	%
Hypercholesterolemia	83	100.0	82	100.0
Women older than 55 years old	58	69.9	58	70.7
Hypertension	52	62.6	51	62.2
Smoking	9	10.8	8	9.8
Obesity (kg/m ² ≥ 30)	12	14.5	13	15.9
Diabetes mellitus	17	20.5	12	14.6
Men older than 45 years old	13	15.7	13	15.9
Coronary heart disease (CHD)	10	12.0	13	15.9
Stroke	0	0.0	1	1.2
Concomitant therapy				
Diuretics	34	41.0	36	43.9
ACEI	27	32.5	21	25.6
β-blockers	16	19.3	20	24.4
Oral hypoglycemic drugs	11	13.3	9	11.0
Antiplatelet drugs	10	12.1	11	13.4
Vasodilatadors	5	6.0	8	9.8
Myorelaxants	5	6.0	5	6.1
Benzodiazepines	5	6.0	5	6.1
Calcium blockers	3	3.6	5	6.1
Thyroid hormones	3	3.6	4	4.9

ACEI angiotensin converting enzyme inhibitors

n Number of subjects, (X ± SD) (mean ± standard deviation)

Table 2: Effects on the lipid profile (X ± SD)

Treatment	Baseline	3 months	6 months	9 months	12 months	% change
LDL-C (mmol/L)						
Policosanol	4.50 ± 0.81	3.62 ± 0.60 ^{***}	3.89 ± 0.96 ^{***}	3.20 ± 0.68 ^{***}	3.15 ± 0.64 ^{***}	- 30.0
D-003	4.61 ± 0.72	3.70 ± 0.50 ^{***}	3.75 ± 0.71 ^{***}	3.20 ± 0.77 ^{***}	3.03 ± 0.79 ^{***}	- 34.3 +
Total cholesterol (mmol/L)						
Policosanol	6.50 ± 0.92	5.61 ± 0.59 ^{***}	6.07 ± 1.02 ^{**}	5.34 ± 0.68 ^{***}	5.23 ± 0.66 ^{***}	- 19.5
D-003	6.60 ± 0.88	5.75 ± 0.58 ^{***}	5.93 ± 0.69 ^{***}	5.42 ± 0.82 ^{***}	5.17 ± 0.88 ^{***}	- 21.7
HDL-C (mmol/L)						
Policosanol	1.21 ± 0.16	1.32 ± 0.18*	1.40 ± 0.31 ^{***}	1.40 ± 0.22 ^{***}	1.30 ± 0.33*	+ 7.4
D-003	1.25 ± 0.18	1.39 ± 0.17 ^{***}	1.43 ± 0.30 ^{***}	1.49 ± 0.23 ^{***}	1.40 ± 0.34 ^{***}	+ 12.0 +
Triglycerides (mmol/L)						
Policosanol	2.14 ± 0.87	1.81 ± 0.69	2.08 ± 0.80	2.00 ± 1.04	2.13 ± 0.95	- 0.5
D-003	2.02 ± 0.85	1.77 ± 0.56	2.05 ± 0.77	1.95 ± 1.09	2.02 ± 0.83	0.0
LDL-C/HDL-C						
Policosanol	3.77 ± 0.78	2.78 ± 0.60 ^{***}	2.89 ± 0.89 ^{***}	2.35 ± 0.62 ^{***}	2.64 ± 0.99 ^{***}	- 30.0
D-003	3.76 ± 0.69	2.71 ± 0.50 ^{***}	2.76 ± 0.84 ^{***}	2.22 ± 0.71 ^{***}	2.30 ± 0.82 ^{***}	- 38.8 ++
TC/HDL-C						
Policosanol	5.44 ± 0.91	4.31 ± 0.67 ^{***}	4.49 ± 1.06 ^{***}	3.92 ± 0.80 ^{***}	4.33 ± 1.33 ^{***}	- 20.4
D-003	5.38 ± 0.88	4.19 ± 0.60 ^{***}	4.33 ± 0.98 ^{***}	3.73 ± 0.86 ^{***}	3.89 ± 1.01 ^{***}	- 27.7 +

** p < 0.001 *** p < 0.0001, Comparisons versus baseline (t test for matched samples),

+ p < 0.05, ++ p < 0.01, Comparisons with policosanol (t test for independent samples)



DISCUSSION

This study demonstrates, for the first time, that D-003 (5 – 20 mg/day) (mean dose 10.2 mg/day) administered for long-term (12 months) exhibited a persistent long-term cholesterol-lowering efficacy, and was more effective than policosanol (mean dose 13.9 mg/day) for lowering LDL-C, the main study outcome.

Study patients were representative of population amenable to receive lipid-lowering therapy according to their LDL-C, since all patients had lipid coronary risk factors others than HC. Study groups were well balanced for all variables, so that they were homogeneous for comparing the effects of both treatments. Study conduction complied with study protocol and the statistical analysis was performed as planned.

D-003 was more effective than policosanol for lowering LDL-C, the primary efficacy variable, consistent with the findings of a previous short-term (8 weeks) head to head comparative study,³⁹ and with the results of independent studies conducted with D-003³⁶⁻⁴³ and policosanol.¹⁴⁻²²

At study completion, D-003 (mean dose 10.2 mg/day) had lowered LDL-C by 34.3%, a reduction significantly, but mildly, higher than that reached (30.0 %) with policosanol (mean dose 13.9 mg/day). The LDL-C reductions achieved here were generally consistent with those reported for D-003 and policosanol. D-003 administered for short-term has shown to produce significant LDL-C reductions from 20.5 % to 26.1 %.³⁶⁻⁴³

The LDL-C reduction with D-003 was almost 5% greater than that achieved with policosanol, so that the criterion of a superior efficacy of D-003 was not clearly reached. The frequency of responders, however, revealed that D-003 was more effective than policosanol, since more D-003-treated subjects (72/82, 87.8 %) reached LDL-C decreases ≥ 15 % compared with those policosanol-treated (66/83, 79.5%).

Both D-003 and policosanol increased HDL-C, but the effects of D-003 were superior that those of policosanol, as expected. These results also agree with those of the previous short-term comparative study,³⁹ and with those of studies conducted on D-003³⁶⁻⁴³ and policosanol.¹⁴⁻²²

The effects of both D-003 and policosanol on LDL-C, TC, HDL-C and both ratios were significant from the first interim check-up, but responses were generally enhanced at study completion.

Both treatments were safe, not affecting the safety indicators followed during the study. Likewise, the withdrawal rate (3%) was low for a long-term (1 year study), and only one was due to an AE unrelated to the treatment, because it consisted on a hip fracture after a car accident that occurred in a D-003-treated subject.

Also, the frequency of AE was low for a long-term trial, since only 11/165 patients (6.7%) (7 policosanol, 4 D-003) reported some AE. Dengue and hip fracture happening in

1 D-003 and 1 policosanol-treated subject, respectively, were considered not treatment-related because occurred during a dengue outbreak occurring in Havana at the time of the study, and after a car accident (big trauma), respectively. Other AE were considered as possibly treatment-related.

The present results support that D-003 could be a good choice for long-term management of lipid profile in hypercholesterolemic subjects as compared to policosanol, but further studies should support this appreciation.

CONCLUSION

Long-term administration (1 year) of D-003 (mean dose 10.2 mg/day) exhibited a persistent long-term cholesterol-lowering efficacy, and was more effective than policosanol (mean dose 13.9 mg/day) for lowering LDL-C, the ratios of LDL-C/HDL-C and TC/HDL-C and for increasing HDL-C. Both treatments were safe and well tolerated.

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