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Comparative efficacy, safety and tolerability of policosanol *versus* statins in patients with type II hypercholesterolemia: emphasis on muscle function indicators.

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RESUMEN: La reducción de los niveles de colesterol total (CT) y del transportado por las lipoproteínas de baja densidad (LDL-C) reduce la frecuencia de eventos coronarios, de modo tal que las drogas reductoras de colesterol se indican en la prevención de la enfermedad coronaria (EC). Sin embargo, la miopatía y la rabdomiolisis han sido relacionadas con su uso, especialmente con los inhibidores de la HMGCoA reductasa (estatinas). El policosanol es un medicamento hipocolesterolemizante purificado de la cera de la caña de azúcar, el cual inhibe la biosíntesis de colesterol a través de la regulación de la actividad de la HMGCoA reductasa. Ha sido demostrada la satisfactoria eficacia a corto y largo plazo del policosanol (5–20 mg/d), siendo notorio lo excelente de su seguridad y tolerabilidad, ya que hasta la fecha no se han demostrado experiencias adversas (EA) relacionadas con su uso. Sin embargo, considerando sus efectos sobre la biosíntesis de colesterol, resulta conveniente descartar si el policosanol puede inducir EA musculares similares a los inducidos por las estatinas. Este estudio se realizó para comparar los efectos del policosanol y las estatinas en pacientes con hipercolesterolemia (HC) Tipo II, con énfasis en su seguridad y en los efectos sobre los indicadores de la función muscular. Tras un período basal de 4 semanas de dieta hipolipemiante, 411 pacientes que cumplieron los criterios de selección fueron distribuidos para recibir, de modo aleatorio y a doble ciegas, policosanol 10 mg/d or estatinas (lovastatina 20 mg/d o simvastatina 10 mg/d). Las tabletas se ingirieron una vez al día con la cena durante 8 semanas. Los exámenes físicos y de laboratorio fueron realizados en condiciones basales y al culminar el tratamiento, mientras que el interrogatorio de EA y la evaluación de la adhesión al tratamiento se realizaron en la visita final. El policosanol (10 mg/d) administrado durante 8 semanas redujo significativamente ($p < 0.00001$) los niveles de LDL-C (23.3 %), TC (16.5 %) y triglicéridos ($p < 0.0001$) (10.1 %), mientras que las estatinas redujeron similarmente ($p < 0.00001$) las cifras de LDL-C (21.8 %), TC (17.4 %) y triglicéridos ($p < 0.001$) (5.5 %). El policosanol, no así las estatinas, aumentaron significativamente ($p < 0.001$) los niveles de HDL-C (9.6 %). La frecuencia de pacientes que alcanzaron reducciones de las LDL-C ≥ 15 % respecto al nivel basal fue mayor ($p < 0.05$) en el grupo policosanol (144/206, 70.0 %) que en el tratado con estatinas (120/205,58.5 %) Ambos tratamientos fueron bien tolerados. Ninguno de ellos afectó los indicadores físicos de seguridad. El policosanol significativamente redujo ($p < 0.05$) los niveles de aspartato aminotransferasa (AST) y ($p < 0.01$) creatinfosfokinasa (CFK), sin modificar los restantes indicadores de bioquímica sanguínea. Las estatinas incrementaron significativamente ($p < 0.05$) los valores de CFK. Veintiocho (28) pacientes (7 tratados con policosanol y 21 con estatinas) abandonaron el estudio. Los dos pacientes tratados con policosanol causaron baja por EA consistentes en dolor abdominal y edema de los miembros inferiores, respectivamente. Los 11 pacientes tratados con estatinas que abandonaron el estudio se debieron a una EA severa (angina inestable) y otras 10 EA no severas. Tres de ellos reportaron EA muscular (mialgia y/o calambres), 5 sufrieron EA gastrointestinales (dolor abdominal; diarrea, náuseas, malestar gástrico y/o vómitos), 2 experimentaron EA cardiovasculares (arritmia, hipertensión descontrolada), mientras otro paciente refirió mareos y dolor de cabeza. Además, tres de estos pacientes refirieron concomitantemente astenia; erupción de la piel y diabetes descontrolada. La frecuencia de EA en el grupo policosanol (14, 6.8 %) fue menor ($p < 0.05$) que en el grupo tratado con estatinas (29, 14.1 %). Se concluye que la eficacia a corto plazo del policosanol (10 mg/d) para disminuir las LDL-C en pacientes con HC tipo II es similar a la de las estatinas administradas a su dosis de partida. Los efectos de ambos tratamientos sobre el CT y los triglicéridos también resultaron equivalentes. El policosanol, no así las estatinas, incrementaron significativamente los niveles de HDL-C. Ambos tratamientos fueron seguros, pero sólo las estatinas aumentaron los valores de CPK, un indicador de la función mus-

cular. El policosanol fue mejor tolerado que las estatinas según reveló el análisis de las bajas y las EA, incluyendo los reportes de EA musculares. Sin embargo, se requiere realizar estudios de largo plazo que investiguen los efectos del policosanol sobre la función muscular utilizando algoritmos específicos a ese fin para descartar definitivamente el riesgo potencial para inducir estos efectos que implica su uso.

ABSTRACT: Lowering elevated total (TC) and low-density lipoprotein-cholesterol (LDL-C) reduces the frequency of coronary events, so that cholesterol-lowering drugs are indicated to prevent coronary heart disease (CHD). Nevertheless, myopathy and rhabdomyolysis are related with the use of these drugs, mainly with HMGCoA reductase inhibitors (statins). Policosanol is a cholesterol-lowering drug purified from sugar cane wax, which inhibits cholesterol biosynthesis through the regulation of the activity of HMGCoA reductase. Short and long-term satisfactory efficacy of policosanol (5 – 20 mg/d) has been demonstrated, being notorious its excellent safety and tolerability, so that no drug-related adverse experiences (AE) have proven up to date. Nevertheless, considering its effects on cholesterol biosynthesis, it is convenient to discard whether policosanol can induce muscular AE similarly to statins. This study was undertaken to compare the effects of policosanol and statins on patients with Type II Hypercholesterolemia (HC), with emphasis on safety and effects on muscle function indicators. After 4 weeks on a baseline cholesterol-lowering diet period, 411 eligible patients randomly received, under double-blind conditions, policosanol 10 mg/d or statins (lovastatin 20 mg/d or simvastatin 10 mg/d). Tablets were taken once a day with the evening meal for 8 weeks. Physical examination and laboratory tests were done at baseline and study completion, while requests for AE and compliance assessment were done at final visit. Policosanol at 10 mg/d for 8 weeks significantly ($p < 0.00001$) lowered LDL-C (23.3 %), TC (16.5 %) and triglycerides ($p < 0.0001$) (10.1 %), while statins reduced ($p < 0.00001$) LDL-C (21.8 %), TC (17.4 %) and triglycerides ($p < 0.001$) (5.5 %). Policosanol, but not statins, significantly increased ($p < 0.001$) HDL-C (9.6 %). The frequency of patients reaching LDL-C reductions ≥ 15 % was significantly greater ($p < 0.05$) in policosanol (144/206, 70.0 %) than in statins group (120/205,58.5 %) Both treatments were well tolerated. None of them affected physical safety indicators. Policosanol significantly lowered ($p < 0.05$) aspartate aminotransferase (AST) and ($p < 0.01$) creatinphosphokinase (CPK) values, while unchanged other blood biochemistry indicators. Statins significantly ($p < 0.05$) increased CPK levels. Twenty-eight (28) patients (7 policosanol, 21 statin) discontinued from the study, Two policosanol patients withdrew from the trial due to AE consisting of abdominal pain and lower limb edema, respectively. Eleven (11) statin-patients discontinued the study due to a serious AE (unstable angina) and other 10 non-serious AE. Three patients reported muscular AE (cramps and/or myalgia), 5 suffered gastrointestinal disturbances (abdominal pain; diarrhea, nauseas, gastric discomfort and/or vomiting), 2 referred cardiovascular AE (arrythmia, uncontrolled hypertension) and other patient reported dizziness + headache. In addition, three of these patients concomitantly reported asthenia; skin rash and uncontrolled diabetes. The frequency of AE in policosanol (14, 6.8%) was lower ($p < 0.05$) than in statin group (29, 14.1 %). It is concluded that short-term efficacy of policosanol (10 mg/d) to reduce LDL-C in patients with type II HC was similar to that of starting doses of statins. Effects of both treatments on TC and triglycerides were also equivalent. Policosanol, but not statins, significantly increased HDL-C. Both drugs were safe, but only statins increased CPK, an indicator of muscle function. Policosanol was better tolerated than statins as revealed AE and withdrawal analysis, including reports related with muscle-related AE. Nevertheless, long-term studies investtigating policosanol effects on muscle function variables through specific algorithm will be needed to definitively discard its potential risk to induce such effects.

INTRODUCTION

Atherosclerotic vascular disease and its thrombotic complications are the basic pathological process involved in coronary heart disease (CHD) and cerebrovascular disease, both con-sidered within the major causes of mortality and morbidity of adult population world-wide.[1,2] Updated prevention policies are based on the control of modifiable atherosclerotic risk factors to prevent atherosclerosis and its sequelae, such as coronary and cerebrovascular clinical outcomes.[3-5]

Hypercholesterolemia (HC) is considered among the major atherosclerotic risk factors,[6–8] being clinically proven that lowering elevated total (TC) and particularly low-density lipoprotein-cholesterol (LDL-C), reduces morbidity and mortality in primary and secondary prevention patients.[9-14]

Thus, adherence to a step I cholesterol-lowering diet addressed to reduce LDL-C levels below specific targets is the cornerstone of HC management in order.[3–5] Nevertheless, diet alone often is not enough to reach the goals, mainly in patients at high risk, for whom more restricted goals are recommended. Thus, cholesterol-lowering drugs are indicated for these cases.

Among lipid-lowering drugs such as inhibitors of HMGCoA reductase (statins or HMGRI) have emerged as the dominant drug class for HC treatment, since it has been convincingly proven that they prevent coronary and cerebrovascular events in both secondary and primary prevention patients.[8–13] In addition to their ability to reduce LDL-C through the competitive inhibition of the pacemaker enzyme of cholesterol biosynthesis, statins have shown a plethora of beneficial pleiotropic effects that contribute, beyond its lipid-lowering properties, to prevent clinical outcomes.[15-17]

Statins are generally well tolerated and most of statin-related adverse experiences (AE) are mild and transient, being gastrointestinal symptoms the most frequent, but actually the most serious AE arise from cell damage in liver and skeletal muscle.[18 – 21] Thus, effects on liver function can be considered as relatively frequent, since statins induce persistent and dose dependent increases in serum transaminases in approximately 1 % of the patients. Nevertheless, although hepatotoxicity is a statin-related AE more common than myotoxicity, this one may pose a larger risk to induce serious AE such as rhabdomyolysis and can lead to myoglobinuria and acute renal failure.[18 – 25]

Myopathy is broadly defined as any abnormal condition or disease of the muscle tissues, commonly involving skeletal muscle Many drugs can cause myopathy and drug-induced myopathy usually develops insidiously, so that the onset of clinical symptoms can occurs from days to months after exposure to the treatment. Frequently, patients present progressive and generalized muscle weakness, being proximal muscle weakness of the arms and the legs the distinctive symptom. Also, muscle pain (myalgia), cramps and fatigue often are present. [26, 27]

In suspected cases of drug-induced myopathy, serum levels of the cellular content of damaged muscle can be measured, such as creatinphosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, myoglobin, potassium and phosphorum. Although CPK is considered the most sensitive laboratory indicator of muscle function, its low specificity is the main limitation to be used in the diagnosis of drug-induced myopathy, since in these cases CPK may be normal to seriously elevated. In addition, although drug-induced myopathy can increase CPK levels, other causes can induce the same effect.[26-29]

Myopathy has been also defined as the presence of ≥ two clinical symptoms with CPK levels increased > 10 fold. In turn, myalgia is referred to a combination of muscle pain, weakness or tenderness in a proximal or regional pattern with a frequent cramping feeling of the muscle, wherein CPK levels can be normal or justly slightly increased.[30]

The interest on lipid-lowering drugs myopathy has been increased after the voluntary withdrawal of cerivastatin from the US market on 2001 by the manufacturer (Bayer), in agreement with the Food and Drug Administration.[31] Cerivastatin was withdrawn because of reports of fatal and nonfatal rhabdomyolisis occurred in cerivastatin users, which were more frequent than in other statin treated patients. Nevertheless, an analysis of 385 reports in persons using other statins supported the petition of Public Citizen to FDA to issue strong warnings about the myotoxic potential of statins, [32] thus attracting the interest of the public arena.

The onset of myopathies induced by lipid-lowering drugs generally occurs within 2 to 3 months after starting treatment, range from days to years and can be recovered in days to months after stopping drug.[25-29] Statin-treated patients myopathy occurs less frequently (< 0.5 %) than myalgia (1 % - 7 %) or CPK increases (1%) alone. Risk factors associated to statin-induced myopathy include hepatic failure, renal insufficiency, metabolic enzyme inhibition, aging, and concomitant use of other myotoxic agents.

The exact mechanism of statin-induced myopathy has not been fully elucidated. Nevertheless, it may involve the mevalonate dependent reduction of cholesterol precursors, altered cell permeability, specific depletion of ubiquinone (CoQ 10) levels, all of which leads to disturbances in cell energy production. In addition, altered excitation-contraction coupling, decreased membrane fluidity, sarcolemma ionic flux and impaired Ca^{+2} modulation can also play a role.[24]

Policosanol is a mixture of higher aliphatic primary alcohols purified from sugar cane (*Saccharum officinarum, L.*) wax[33, 34] with cholesterol-lowering efficacy proven on patients with type II HC[35-46] and in the dyslipidemia due to Type 2 diabetes.[47-49] Policosanol inhibits cholesterol biosynthesis,[50–52] through a mechanism different from that of statins, since involves an indirect regulation of HMG CoA reductase activity instead of a competitive inhibition. Clinical trials[35 - 49] and postmarketing surveillance studies[53, 54] have shown that policosanol is safe and well tolerated and no drug-related AE has been proven up to date.

Nevertheless, since the inhibition of cholesterol biosynthesis induced by policosanol occurred in a step located between acetate consumption and mevalonate production, myotoxic effect dependent from the reduction of cholesterol precursors and particularly, from ubiquinone depletion, cannot be excluded, although have not been demonstrated.

Taking into account such background, this study was undertaken to investigate whether policosanol short-term administered to patients with Type II HC induces AE related with muscle function impairment, compared with those induced by statins. In addition, short-term efficacy of both treatments was also compared.

PATIENTS AND METHODS

Study design.

The present study was short-term, randomized, double-blind, parallel-group and comparative *versus* statins. After 4 weeks on cholesterol-lowering diet, 411 patients randomly received policosanol 10 mg/d or statins (lovastatin 20 mg/d or simvastatin 10 mg/d) for 8 weeks.

At recruitment (visit 1) patients entered in a 4 week run-in period, during which they discontinued all lipid-lowering therapy and were instructed to follow a step I cholesterol-lowering diet. [4, 6] After this diet-only period study, two consecutive lipid profile determinations were done within 15 days. In the occasion that samples for the second determination were drawn, aliquots for safety laboratory tests were done.

Eligible patients were randomized, under double-blind con-

ditions, to policosanol (10 mg), lovastatin (20 mg) or simvastatin (10 mg) tablets. Study medications were randomized by a fixed randomization method using a block size of 12 and allocation ratio 1:2, thus considering both statins as a whole group for analysis. Lovastatin 20 mg and simvastatin 10 mg-tablets purchased from Merck Sharp Dohme, (Spain) were used and policosanol 10 mg-tablets were manufactured to offer similar appearance to that of statins. Patients were instructed to take study medications once a day with the evening meal for 8 weeks.

Study patients

Patients from both sexes, aged 38 to 75 years old, and showing documented Type II HC were enrolled in the study. All patients provided written informed consent before enrolling the trial. They met inclusion criteria if their LDL-C and TC values after the diet-only period were ≥ 3.4 mmol/L and 5.2 mmol/l, respectively. Trigly-cerides should be < 4.52 mmol/L to can apply Friedewald Equation for LDL-C calculation.[55]

Patients with active renal or hepatic diseases, diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg) and uncontrolled diabetes (glucose > 7.5 mmol/L) were excluded from the study. In addition, those who had had unstable angina, myocardial infarction, stroke, transient ischemic attacks or coronary surgery within the 3 months previous to the study were also excluded.

Assessments

At recruitment (visit 1), a complete medical history including physical examination was performed. In the short-term study, physical examination and laboratory tests were done at baseline (visit 2) and after 8 weeks (visit 3) on treatment, meanwhile request for adverse experiences (AE) and assessment of compliance with study medications were done at visit 3. Drug compliance was assessed by tablet count and patient's interview.

Laboratory analysis

Blood samples were drawn from 8:00 to 8:30 a.m. after an evening fasting of 12 hours and aliquots were obtained for laboratory determinations. TC and triglycerides were determined by colorimetric enzymatic methods using reagent kits from Boerhinger Mannheim (Germany). Levels of HDL-C were determined according to the cholesterol content present in the supernatant obtained after β-lipoproteins precipitation.[56] LDL-C values were calculated using the Friedewald equation.[55]

Laboratory safety tests included determinations of glucose, creatinine, AST, ALT and CPK were performed by routine laboratory tests based in colorimetric enzymatic methods using reagent kits from Boehringer Mannheim, Germany. Laboratory tests were performed in the Hitachi 712 autoanalyzer (Tokyo, Japan) located at the laboratory of the Center for Surgical and Medical Research (Havana City, Cuba).

A systematic quality control was performed throughout the study, so that the precision and accuracy of the methods was followed. Precision was assessed according to repeatability (r) (within-day variations) and reproducibility (R) (between-day variations); meanwhile accuracy was evaluated against standard references. Taking into account that the main efficacy variable (LDL-C) was calculated by Friedewald equation, the quality of the determination of the lipid parameters included in such Equation was the main target of quality control. The coefficient variations were TC: r = 2.7; R=3.1; Triglycerides r = 3.7, R = 4.0; HDL-C r = 3.0; R = 3.5. The differences against the standard reference were < 4% for TC and < 5% for triglycerides.

Efficacy variables

Changes on LDL-C levels were considered as primary efficacy variable. The treatments were considered as effective only if LDL-C levels were reduced by at least 15 % compared with baseline.[57] Another lipid profile variables were considered as secondary efficacy variables.

Safety and tolerability

Data from physical examination, laboratory tests and interview for AE were included for the analysis of drug safety and tolerability. AE predefined as “serious” were fatal or disabling events, leading to or prolonging hospitalization. AE predefined as “moderate” were those requiring therapy discontinuation according to the physician and/or specific treatment of the AE. Those AE not requiring discontinuation of study drugs and/or specific treatment were classified as “mild”.

The AE were also classified as unlikely, doubtfully, possibly or probably drug related according to their probable relationship with study medications. Since the classification of an AE as definitively drug-related requires the challenge of the study drug and the suspension of treatment was predefined as a cause of withdrawal, this concept was not applied to the AE occurred during the study.

Statistical analysis

All data were analyzed according to the Intention-to-Treat approach, it means that available data of withdrawals were included in all analysis.

Within group comparisons of continuous variables were performed using the Wilcoxon test for paired samples; meanwhile between group comparisons were done using the Mann Whitney U Test. Comparison of categorical variables were done using the Fisher's Exact Test. All tests were two tailed. A value of $\alpha = 0.05$ was assumed for statistical significance. Statistical analyses were performed using the Statistica for Windows package program.

RESULTS

Baseline characteristics

Of the 411 randomized patients, 382 (92.9 %) completed the short-term study. Both groups were comparable at randomization respect all characteristics (Table 1). The

Table 1. Baseline characteristics of study patients

Characteristics	Policosanol (n = 206)		Statins (n = 205)	
Age (years) (X ± SD)	59 ± 12		59 ± 10	
Body mass index (kg/m^2) (X ± SD)	27,3 ± 3,9		26,8 ± 3,9	
Sex: Female n (%)	154	74,8	148	72,2
Male n (%)	52	25,2	57	27,8
Subtype of Type II HC n (%)				
II a or isolated HC	126	61,1	125	61,0
II b or combined HC	80	38,8	80	39,0
Personal risk factors: n (%)				
Postmenopausal women	101	49,0	108	52,7
Male older than 45 years old	48	23,3	52	25,4
Hypertension	51	24,8	43	21,0
Smoking	19	9,2	15	7,3
Secondary prevention	12	5,8	11	5,3
Diabetes mellitus	4	1,9	7	3,4
Concomitant medications (CM) n (%) *	30	14,6	27	13,2
Diuretics	11	5,3	10	4,9
Angiotensin Converting Enzyme inhibitors	6	2,9	6	2,9
β-blockers	5	2,4	6	2,9
Calcium antagonists	5	2,4	5	2,4
Vitamins	|5	2,4	5	2,4

n Number of patients; (X ± SD) (mean ± standard deviation)
*The table includes only those CM consumed by ≥ 2 % of study patients

withdrawals will be analyzed in the section of safety and tolerability. With the exception of arterial hypertension, which showed a frequency greater than 20 %, the frequency of other modifiable risk factor was relatively low. Consequently, diuretics, angiotensin converting enzyme inhibitors (ACEI), β - blockers and calcium antagonists were the concomitant drugs more consumed during the trial, although their the total consumption was lower than the frequency of hypertensive subjects reported, indicating that many of them were controlled by diet and physical exercise.

Effects on lipid profile

Table 2 shows the effects of policosanol and statins on lipid profile; both groups being similar at baseline. After 8 weeks on therapy, policosanol at 10 mg/d significantly ($p < 0.00001$) lowered LDL-C, the main efficacy variable, by 23.3 %, TC by 16.5 % and triglycerides ($p < 0.0001$) by 10.1 % compared with baseline. In turn, statins reduced ($p < 0.00001$) LDL-C by 21.8 %, TC (17.4 %) and triglycerides ($p < 0.001$) (5.5 %). Policosanol, but not statin, significantly increased ($p < 0.001$) HDL-C by 9.6 %, this change being different ($p < 0.01$) from that occurred in statin group.

The frequency of randomized patients reaching LDL-C reductions ≥ 15 % respect to baseline was significantly greater ($p < 0.05$) in policosanol (144/206, 70.0 %) than in in statin group (120/205, 58.5 %).

Safety and tolerability

Safety indicators determined throughout the physical examination of the patients were unaffected by policosanol or statins (Table 3). Regarding to blood biochemistry indicators, policosanol significantly lowered ($p < 0.05$) AST and ($p < 0.01$) CPK values compared with baseline, whereas it did not change any other safety indicator. By contrast, statins significantly ($p < 0.05$) increased CPK levels. Comparisons between groups revealed that final values of AST and CPK were lower ($p < 0.05$) in policosanol than in statin group.

Twenty-eight (28) patients (7 policosanol, 21 statin-treated) discontinued from the study. Thus, the withdrawals from policosanol group were due to change of address (1 patient); unwillingness to follow-up (4) and moderate AE (2) consisting on abdominal pain and lower limb edema.

Table 2. Short-term effects of policosanol (10 mg/d) and statins (10 mg/d) on lipid profile (X ± SD) of patients with type II HC

Treatment	Baseline	8 weeks	% changes
LDL-C (mmol/L)			
Policosanol	4,80 ± 0,86	3,67 ± 0,83***	**- 23,3**
Statins	4,90 ± 0,88	3,77 ± 0,95***	**- 21,8**
TC (mmol/L)			
Policosanol	6,94 ± 0,71	5,77 ± 0,89***	**- 16,5**
Statins	7,00 ± 0,96	5,80 ± 1,04***	**- 17,4**
HDL-C (mmol/L)			
Policosanol	1,30 ± 0,33	1,38 ± 0,33****++	**+ 9,6**$^{+++++}$
Statins	1,34 ± 0,35	1,28 ± 0,30*	**- 1,7**
Triglycerides (mmol/L)			
Policosanol	2,22 ± 0,85	1,85 ± 0,72****	**- 10,1**
Statins	2,18 ± 0,81	1,95 ± 0,85***	**- 5,5**

X mean, SD standard deviation; % Percent changes
*p < 0.05; **p < 0.01, ***p < 0.001 ****p < 0.0001, *****p < 0.00001 Comparison with baseline
++p < 0.01; +++p < 0.001, ++++p < 0.0001; +++++p < 0.00001 Comparison with placebo

In turn, the 21 discontinuations on statin group were related with changes of address (1), protocol violation (1), unwillingness to follow-up (8) and AE (11). The AE causing the 11 withdrawals were a serious AE (angina) (1 patient) and other 10 AE. These other 10 AE were du to pneumonia (1); muscle cramps (1); gastritis (1); myalgia and abdominal pain (1), myalgia, arrythmia and asthenia (1); diarrhea and vomiting (1), skin rash and gastrointestinal discomfort) (1); uncontrolled hypertension and diabetes, (1); uncontrolled hypertension, dizziness and headache (1). Overall, the frequency of policosanol patients reporting some AE (14, 6.8 %) was lower ($p < 0.05$) than in the statin group (29, 14.1 %) (Table 4). Likewise, the same was true for the total of AE reported, which were 15 (7.3 %) in policosanol and 46 (22.4 %) in statin group ($p < 0.0001$).

DISCUSSION

The present study demonstrates that policosanol short-term administered at 10 mg/d reduces LDL-C, TC and triglycerides similarly as statins in patients with type II HC, but inducing beneficial effects on HDL-C levels. Thus, the average decreases on LDL-C, the main efficacy variable, were similar in policosanol (23.3 %) and statin groups (21.8 %) and the same was true for the reductions in TC and triglycerides. The comparison of the frequency of responders, however, showed a mild advantage for policosanol group. Thus, the frequency of randomized patients reaching LDL-C reductions ≥ 15 % were 70.0 % for policosanol and 58.5 % for statin, accounting for a frequency approximately 12 % greater in policosanol than in statins. These therapeutic responses generally agree with those reported for similar doses of policosanol[38-44] or statins.[40,42, 44, 49] In particular, the relative advantage of policosanol to increase HDL-C levels compared with statins is on line with previous results obtained in some other comparative studies versus pravastatin,[38,42] lovastatin[40,49] and fluvastatin.[44] Thus, the response of HDL-C agrees with that observed in most studies, although the extent of the change has changed in different studies.

The changes on triglycerides, however, are within the reported range for both drugs, must it must be pointed that such response has been highly variable for policosanol and statins, so that in some studies they have lowered significantly, while in other have remained unchanged.

Both policosanol and statin did not impair safety indicators measured during physical examination. Policosanol modestly, but significantly reduced AST, which corroborates its lack of hepatotoxicity, while also decreased CPK levels, a finding consistent with some previous reports. All individual values remained within normal limits, which limits the clinical relevance of these changes. Statins significantly, but moderately increased CPK values, so that only 3 patients experienced increases of CPK more than 3 times above the upper normal limit.

Policosanol was better tolerated than statins, as reflected withdrawals due to AE and AE reports occurred during the study, which is consistent

Table 3. Short- term effects of policosanol and statins on safety indicators (X ± SD) on patients with type II HC

Treatment	Baseline	Week 8
	Body weight (kg)	
Policosanol	69,06 ± 10,51	68,53 ± 10,29
Statins	70,02 ± 11,79	70,07 ± 12,14
	SBP (mm Hg)	
Policosanol	134,89 ± 17,33	133,19 ± 17,09
Statins	135,76 ± 16,93	135,96 ± 16,78
	DBP (mm Hg)	
Policosanol	81,84 ± 9,23	81,73 ± 8,42+
Statins	82,33 ± 9,81	83,56 ± 8,51
	ALT (U/L)	
Policosanol	18,47 ± 8,63	18,41 ± 8,09
Statins	19,85 ± 8,68	19,99 ± 9,28
	AST (U/L)	
Policosanol	19,16 ± 8,26	18,26 ± 6,72*+
Statins	19,99 ± 8,08	19,84 ± 8,37
	CPK (UI/L)	
Policosanol	94,54 ± 54,63	81,71 ± 46,41****+
Statins	94,58 ± 59,93	107,55 ± 71,40*
	Glucose (mmol/L)	
Policosanol	5,38 ± 1,16	5,31 ± 1,58
Statins	5,37 ± 1,38	5,46 ± 1,90
	Creatinine (μmol/L)	
Policosanol	91,09 ± 15,02	91,40 ± 16,20
Statins	91,10 ± 17,60	92,74 ± 17,91

HC hypercholesterolemia, X mean, SD standard deviation; nt not tested
*p < 0.05; **p < 0.01; ***p < 0.001, ****p < 0.0001, ***p < 0.00001 Comparison with baseline
+p < 0.05 ++p < 0.01, +++p < 0.001 Comparison with statins

with the safety and tolerability profile documented for both classes of drugs. Thus, 11 statin and only 2 policosanol patients discontinued from the study, all because of AE. With the exception of the serious AE occurred in statin group (*angina pectoris*) all other AE were, in principle, considered as drug-related since they are within those expected from the safety and tolerability profile of these drugs.

As observed, those AE that can be considered as manifestations of myophaties, such as myalgia and muscle cramps, were only reported by statin-treated patients. This fact, together with the detected increase on CPK levels in this group is within the expected effects of statins on muscle function. In contrast, no report of myalgia, muscle cramps or or any other myopathy symptom was reported in policosanol group, being observed a decrease of CPK values without conclusive explanation, but clearly indicative that no impairment of such indicator was induced by policosanol treatment.

This differential effects of both drugs, particularly on skeletal muscle indicators could be suprising at a first glance since both of them in-

Table 4 Adverse experiences (AE) reported during the study

AE	Intensity	Policosanol (n = 206)		Statins (n = 205)	
		n	%	n	%
Nervous system					
Dizziness	Mod	0	0,0	1	0,5
	M	3	1,5	0	0,0
Headache	Mod	0	0,0	1	0,5
	M	2	1,0	2	1,0
Nervousness	M	2	1,0	0	0,0
Paresthesia	M	0	0,0	1	0,5
Subtotal		**7**	**3,5**	**5**	**2,4**
Cardiovascular					
Uncontrolled hypertension	Mod	0	0,0	2	1,0
Lower limbs edema	Mod	1	0,5	0	0,0
	M	0	0,0	1	0,5
Unstable angina	S	0	0,0	1	0,5
Arrythmia	Mod	0	0,0	1	0,5
Dyspnea at effort	M	0	0,0	1	0,5
Chest pain	Mod	0	0,0	1	0,5
Tachycardia	M	0	0,0	1	0,5
Subtotal		**1**	**0,5**	**8**	**4,0**
Gastrointestinal					
Abdominal pain	Mod	1	0,5	2	1,0
	M	2	1,0	1	0,5
Nauseas	Mod	0	0,0	1	0,5
	M	1	0,5	4	2,0
Diarrhea	Mod	0	0,0	1	0,5
	M	0	0,0	2	1,0
Dyspepsia	M	2	1,0	0	0,0
Meteorism	M	0	0,0	3	1,5
Vomiting	Mod	0	0,0	1	0,5
	M	0	0,0	1	0,5
Abdominal discomfort	M	0	0,0	2	1,0
Gastritis	Mod	0	0,0	1	0,5
Acidity	M	0	0,0	3	0,5
Bite taste	M	0	0,0	1	0,5
Subtotal		**6**	**2,5**	**23**	**11,3**
Muscular					
Myalgia	Mod	0	0,0	2	1,0
Muscle cramps	M	0	0,0	1	0,5
Subtotal		**0**	**0,0**	**3**	**1,5**
Body as a whole					
Asthenia	Mod	0	0,0	1	0,5
	M	1	0,5	1	0,5
Sweat	M	0	0,0	1	0,5
Subtotal		**1**	**0,5**	**3**	**1,5**
Metabolism					
Uncontrolled diabetes	Mod	**0**	**0,0**	**1**	**0,5**
Respiratory					
Pneumonia	Mod	**0**	**0,0**	**1**	**0,5**
Skin and appendages					
Skin rash	M	**0**	**0,0**	**2**	**1,0**
Total of AE reported		**15 (7,3 %)**	**46 (22,4 %)**	**P < 0,00001**	
Total of patients reporting AE		**14 (6,8 %)**	**29 (14,1 %)**	**P < 0,05**	

S serious, Mod moderate, M Mild, Comparison between groups (Fisher's Exact probability test)

hibits cholesterol biosynthesis at a step between acetate consumption and mevalonate production. All these toxic effects induced by statins have been associated with their mechanism of action due to the reduction of mevalonate content.[24] Nevertheless, in the case of the statins this effect is reached by a direct and marked competitive inhibition of HMGCoA reductase, while in the case of policosanol such inhibition is achieved by a moderate regulation of enzyme activity. This difference looks to the cause of the differences in the safety and tolerability profile of both drugs.

However, since cholesterol-lowering therapy must be chronically administered, the duration of this study was short for conclusions in the comparison of safety and tolerability of both drugs, which needs long-term comparative studies.

CONCLUSIONS

Policosanol short-term administered at 10 mg/d was as effective as statins to reduce LDL-C, TC and triglycerides on patients with type II HC. Policosanol, but not statins, significantly increased HDL-C. Both drugs were safe, but only statins increased CPK, an indicator of muscle function. Policosanol was better tolerated than statins as revealed withdrawals analysis and overall frequency of AE. In particular, AE related with muscle function, such as myalgia and muscle cramps, were reported by 3 statin patients (1.5 %), but not in policosanol group. Nevertheless, further long-term studies assessing specific algorithm to discard disturbances on muscle function must be conducted to reach wider conclusions.

Nevertheless, further long-term studies assessing specific algorithm to discard disturbances on muscle function must be conducted to definitively discard any myotoxic potential of policosanol.

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