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Efficacy and safety of a combination of red yeast rice and olive extract in hypercholesterolemic patients with and without statin-associated myalgia

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ABSTRACT

Cholesfytol®, a lipid-lowering dietary supplement with antioxidant and anti-atherosclerotic properties, combines red yeast rice (RYR) and olive extract (5 mg hydroxytyrosol equivalent) and represents an alternative for patients who do not wish or are unable to use chemical statins, including individuals with previous statin-associated muscle symptoms (SAMS). A 2-months observational non-randomized study was performed to evaluate the efficacy, tolerance and safety of Cholesfytol® (1 tablet/day) in 642 hypercholesterolemic patients (mean age: 59 yrs; total cholesterol (TC) ≥200; LDL-C ≥140 mg/dl). Patients were followed by 126 GPs, and included irrespective of SAMS history and/or diabetes. None of the patients were taking statins or other lipid-modifying therapy at inclusion. At baseline, 26% had fasting glucose > 100 ≤125 mg/dL, and 5% > 125 mg/dL; 32% (n = 194) had a SAMS history; and 21% had atherogenic dyslipidemia (AD). In the entire cohort, pre-treatment TC; non-HDL-C; LDL-C; and TG were 259; 200; 168; 158 mg/dL, respectively, and decreased significantly on treatment (−17.5% (TC) and −23.3% (LDL-C)). Fasting glucose and HbA_{1c} decreased between visits. The reduction in lipids was greater in patients with higher values at baseline. For comparable pre-treatment values, patients with SAMS history had reductions in TC, LDL-C, non-HDL-C, and $apoB_{100}$ slightly less than patients without myalgia. AD patients had greater on-treatment decrease in TG. Overall, 13 patients reported minor side-effects, and 4 patients reporting myalgia had antecedent SAMS. In conclusion, a substantial decrease in LDL-C was obtained with a combination of RYR and olive extract in high-risk hypercholesterolemic patients, without inducing new-onset SAMS.

1. Introduction

High cholesterol is a major modifiable cardiovascular (CV) risk factor. There is compelling evidence that increased levels of cholesterol bound to low-density lipoprotein (LDL) are associated with higher incidence of large vessels disease, *via* the accumulation of cholesterol within atherosclerotic plaques of coronary and cerebral arteries. LDL particles, especially the small-dense ones, more susceptible to oxidation, are directly involved in the formation of the atheromatous plaque. Landmark clinical trials have shown indisputably the clinical benefit of a reduction of LDL-cholesterol (LDL-C) levels, with statins (natural or synthetic *3-hydroxy-3-methyl-glutaryl-CoA* [HMG-CoA] *reductase* inhibitors) as preferred agents, for reducing CV outcomes in patients with elevated LDL-C. This lead to recommend targeting LDL-C levels < 70 and < 100 mg/dL with statins (± ezetimibe) for primary or secondary prevention, respectively. More recently, it was demonstrated that even greater lowering of LDL-C provides additional gain in terms of CV outcomes, justifying a “lower the better” and “lowest the best” approach regarding the intensive treatment of hypercholesterolemia in subjects with high CV risk.[1–9]

Abbreviations: AD, atherogenic dyslipidemia; $apoB_{100}$, apolipoprotein B_{100}; CHD, coronary heart disease; $_{hs}$CRP, high-sensitivity C-reactive protein; CV, cardiovascular; DM, diabetes mellitus; GP, general practitioner; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; NS, non-significant; RYR, red yeast rice; SAS®, statistical Analysis System®; SD, standard deviation; SAMS, statin-associated muscle symptoms; TC, total cholesterol; TG, triglycerides (triacylglycerols)

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Besides 1st, 2nd & 3rd generation prescription statins, whose average effects are predictable, many food supplements containing statins, naturally-present in some fermented foods and condiments, are sold over-the-counter to consumers wishing to reduce their cholesterol without resorting to prescription drugs. Of these, red yeast rice (RYR) extract is at the forefront. Traditionally used as colouring, flavouring, additive, preservative or condiment, RYR contains lipid-lowering compounds naturally synthesized by *Monascus purpureus* (Went 1895) and related yeasts. Efficacy and outcomes studies have showed unambiguously the clinical efficacy of RYR extracts in humans. Monacolin K is the principal *HMG-CoA reductase* inhibitor of RYR, with a bioavailability higher than that of lovastatin.[10–14]

Cholesfytol® (Tilman SA, Belgium) is a citrinin-free 2nd generation lipid-lowering dietary supplement of mixed origin (plant and fungal), consisting of RYR extract (240 mg *Monascus purpureus* powder (equivalent to 10 mg Monacolin K]) and 25 mg of olive fruit dry extract (*Olea europaea*) [equivalent to 5 mg of hydroxytyrosol]). The latter, a polyphenol compound present in the fruits and leaves of *Olea europaea*, is found at high concentration in olive mill waste waters. *In vitro* and *in vivo* studies have shown that hydroxytyrosol exerts antioxidant effects (including prevention of LDL oxidation), with putative anti-atherosclerotic and anti-ischemic properties.[19] The association of RYR extracts and hydroxytyrosol is an alternative for patients who do not wish, or are unable for various reasons, to use chemical statins to decrease low-density lipoprotein cholesterol (LDL-C). A substantial portion of these patients are individuals who previously experienced statin-associated muscle symptoms (SAMS), particularly myalgia, with the result that they completely stopped taking their prescribed statins.[12,15–18,20,21] The present study was performed to evaluate the therapeutic efficacy, tolerance and safety of Cholesfytol® in hypercholesterolemic patients with or without a history of statin-associated myalgia receiving usual care in general practice and yet not treated with medicines or dietary supplements targeting lipids and lipoproteins.

2. Patients and methods

This observational, non-randomized study was conducted among general practitioners (GPs). Inclusion and exclusion criteria were: patients with no statin treatment or who discontinued statin intake one month before the start of the study; no other lipid-modifying therapy (including dietary supplements and tablets containing RYR) and/or fibrates and/or resins and/or ezetimibe; total cholesterol ≥200 mg/dl; LDL-C ≥140 mg/dl; and age ≥21 years. Patients with or without myalgia/SAMS history and/or diabetes were eligible. Pregnant or lactating women were not includable. A questionnaire was completed by the GP at the first visit (Visit 1), after which treatment was initiated with 1 daily tablet of Cholesfytol® taken in the evening. The patients were reviewed by the same GP after 2 months (Visit 2), and another questionnaire was completed at the second visit.

Data collected during the baseline visit were: age; sex; current or past use of glucose-lowering drugs, lipid-modifying drugs (LMD), or other cardiovascular drugs; history of myalgia (*yes/no*); total cholesterol (TC); LDL-C (*calculated from Friedewald's formula*); HDL-C; non-HDL-C (TC *minus* HDL-C); ultra-sensitive CRP ($_{hs}$CRP); fasting glucose; and glycated (HbA_{1c}; %). Data collected during visit 2 (after 2 months) were TC; LDL-C; HDL-C; non-HDL-C; $_{hs}$CRP ultra-sensible; fasting glucose; HbA_{1c}; side effects (*yes/no*; if yes, which ones); would you continue treatment (*yes/no*). Atherogenic dyslipidemia (AD) was defined as the combination of low HDL-C (< 40 mg dL^{-1} (males); < 50 mg dL^{-1} (females)) and high fasting TG (≥150 mg dL^{-1} for both genders), based on metabolic syndrome cutoffs for non-LDL lipids.[22] Apolipoprotein B_{100} ($apoB_{100}$) level was derived from non-HDL-C using a previously published equation.[23] LDL size was estimated using the LDL-C/$apoB_{100}$ ratio.[24,25]

For quantitative variables, results are expressed as mean ± 1 standard deviation (SD). They are presented in frequency tables (percent) for categorized variables. Statistical analysis was performed on the « intention-to-treat » population. For assessing therapeutic efficacy, the difference between visit 1 and visit 2 is presented in mean value and/or percentage change compared to baseline. Changes were evaluated using Student *t* test for paired samples. The analysis of factors influencing treatment effectiveness was performed using linear regression models on modifying cholesterol levels between the two visits. The results were considered significant at 5% uncertainty level. Statistical analyzes were performed using SAS software (Version 9.4) and R (version 3.0.3). The study was performed in agreement with the principles of the Declaration of Helsinki and Good Clinical Practice.

Table 1
Patients' characteristics at baseline.

	n (%)	mean (SD)
age (years)	642	59 (12)
gender		
male	289 (45)	
female	353 (55)	
history of statin-induced myalgia		
yes	194 (32)	
no	407 (68)	
lipids and lipoproteins		
total cholesterol (mg/dl)		259 (27)
non-HDL-C (mg/dL)		200 (28)
LDL-C (mg/dL)		168 (25)
HDL-C (mg/dL)		59 (17)
triglycerides (mg/dL)		158 (56)
$apoB_{100}$ (mg/dL)		136 (20)
LDL size [LDL-C/$apoB_{100}$]		1.23 (0.17)
atherogenic dyslipidemia	132 (21)	
metabolic markers		
$_{hs}$CRP (mg/L)		6 (21)
glycemia (mg/dL)		99 (22)
HbA_{1c} (%)		6.4 (1.2)

apoB: apolipoprotein B; hsCRP: high-sensitivity C-reactive protein; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation.
Results are expressed as means (SD) or proportions (%). ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BB: beta-blocker; CCB: calcium-channel blocker; CHD: coronary heart disease; DRP: diabetic retinopathy; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HOMA: homeostatic model assessment; Met: metformin; PNP: peripheral neuropathy. NS: non-significant.

3. Results

One hundred and twenty six GPs participated in the study, with 642 patients recruited between March 2013 and June 2014. The average number of patients per GP was 5 ± 3, with a median number of 5 [range 1–18 patient(s)]. Table 1 shows the characteristics of patients at baseline (first visit (V1)). Mean (1 SD) age was 59 (12) years [range 21–89 years]. The population consisted of 45% men. None of the patients was treated with medicines or dietary supplements targeting lipids and lipoproteins at V1. The history and clinical data showed that 32% (n = 194) had a previous history of SAMS, such a history of myalgia having being available in 601 patients (94%).

At V1, mean total cholesterol (TC) was 259 mg/dL [range 199–381], non-HDL-C 200 mg/dL, [115–337] LDL-C 168 mg/dL,[78–311] HDL-C 59 mg/dL, [21–3821–123] and triglycerides 158 mg/dL. [29–3829–267] Mean $apoB_{100}$ was 136 (20) mg/dL,[115–229] and LDL size (LDL-C/$apoB_{100}$) 1.23 (0.17) [0.98–2.32]. Regarding $_{hs}$CRP, 17% of patients had high (> 5 mg/L) baseline value, whereas 26% had fasting glucose at V1 > 100 and ≤125 mg/dL, and 5% had fasting glucose > 125 mg/dL. Among the 113 patients with glycated haemoglobin measurement available at baseline, 29 (25.7%) had HbA_{1c} > 7.0%. Following V1,