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The combination of nutraceutical and simvastatin enhances the effect of simvastatin alone in normalising lipid profile without side effects in patients with ischemic heart disease☆

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ABSTRACT

Background: hyperlipidemia is one of the most important cardiovascular risk factors. Statins at high doses are commonly prescribed to lower LDL-cholesterol, but are often poorly tolerated. In particular, muscle pain and increase of creatine phosphokinase are frequent side effects. The purpose of this study was to assess whether the addition of a nutraceutical to simvastatin may result in the achievement of the therapeutic target (LDL-cholesterol less than 70 mg/dL) without side effects in patients with ischemic heart disease.

Methods: Sixty-four patients with ischemic heart disease treated with simvastatin 20 mg who had not achieved the therapeutic target were enrolled. Patients were randomised 1:1. Patients of group A (n = 32) were given simvastatin 40 mg per day and patients of group B (n = 32) were given simvastatin 20 mg plus 2 tablets of a nutraceutical composed of bergamot, phytosterols, artichoke, vitamin C.

Results: After 3 months, patients in both groups showed a significant reduction from baseline in total cholesterol, LDL-c and tryglicerides. However, in group A, 4 patients reported myalgia (9,7%) with an increase in creatine phosphokinase; whereas no adverse events occurred in group B.

Conclusions: The association of a nutraceutical and simvastatin 20 mg may be a valid therapeutic option for the treatment of hyperlipidemia in patients with ischemic heart disease intolerant to statin at high doses, in the absence of side effects. Further studies are needed to clarify the mechanisms of action of nutraceuticals.

1. Introduction

Hyperlipidemia is one of the most important cardiovascular risk factors, associated to the development of several diseases such as atherosclerosis [1], coronary heart disease (CHD) [2], cerebrovascular ischemia and peripheral vascular disease [3].

Although the incidence of events related to cardiovascular disease is declining in the western world [4], the latter is still the major cause of morbidity and mortality of adults of average age and advanced age [5]. Further, the incidence and absolute number of events per year will probably tend to increase in the next decade because of the rise in obesity and the population aging [6,7].

Relatedly, increased blood concentrations of total cholesterol, low density lipoprotein cholesterol (LDL-c) and triglycerides, often accompanied by low levels of high density lipoprotein-cholesterol (HDL-c) comprise the main pathogenic risk profile. Also, genetic abnormalities and lifestyle (physical inactivity, diets high in calories, fatty acids and cholesterol) contribute to the development of dyslipidemia, frequent in developed countries [8,9]. Therefore, it is well known that treating hypercholesterolemia reduces cardiovascular mortality and morbidity.

To date, EAS/ESC [10] and ACC/AHA [11] guidelines identify statin drugs as the mainstay of therapy for hypercholesterolemia and for the prevention of cardiovascular risk. For these reasons, the majority of therapeutic protocols rely on these drugs.

Statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, which catalyses an early and rate-limiting step in cholesterol biosynthesis [12,13].

Statins are able to lower the levels of LDL-c from 20% to 55% depending on the dosage and the statin used [14]. Although statins exert clearly their main effects on CHD by lowering the levels of LDL-c and improving

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lipid profile, a number of other potentially cardioprotective effects have been attributed to these drugs, such as the improvement of endothelial function, the action on plaque stability and inflammation, reducing levels of C-reactive protein and decreasing the risk of CHD [15,16]. Moreover, a decrease of 43% of thromboembolic events in patients treated with a statin has been observed [17].

Among drugs currently marketed, statins are the most effective and better tolerated agents for the treatment of dyslipidemia [18,19]. The latest EAS/ESC guidelines indicate that in patients with ischemic heart disease the therapeutic target for the levels of LDL-c is less than 70 mg/dL. This goal is reached only in patients who were prescribed statins at high doses.

However, it is well known in clinical practice that taking statins at high doses is often poorly tolerated for the occurrence of side effects such as muscle pain and increase of creatine phosphokinase (CPK) [20].

Moreover, despite the significant clinical benefits provided by statin therapy, many patients do not achieve their recommended levels of LDL-c and HDL-c with statins alone [21].

The onset of side effects and the importance of achieving the therapeutic target in patients at risk of cardiovascular events suggest the need to find alternative therapeutic approaches.

Experimental and epidemiological evidence suggests that dietary polyphenols, in particular flavonoids, may play a role in ameliorating atherosclerosis, due to a pleiotropic anti-oxidative and anti-inflammatory effect proposed as underlying mechanism [22].

In particular, Bergamot (*Citrus bergamia Risso et Poiteau*), an endemic plant growing in the Calabrian region of Southern Italy, has a unique profile and a high content of flavonoids and glycosides in its juice and albedo such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, poncirin [23,24].

Moreover, bergamot juice has been found to be rich in 3-hydroxy-3-methylglutaryl neohesperidosides of hesperetin (brutieridin) and naringenin (melitidin) [25] which demonstrated their activity on inhibiting HMG-CoA reductase, both in animal models of diet-induced hyperlipidemia [26], and in patients suffering from hyperlipidemia, hyperglicemia and metabolic syndrome [27] showing a clear effect on total-cholesterol, LDL-c, HDL-c, tryglicerides and glucose blood levels.

Recently, the activity of bergamot juice flavonoids has been evaluated in comparison to a statin in patients with metabolic syndrome, showing that the addition of bergamot poliphenolic fraction (BPF) to rosuvastatin significantly enhanced rosuvastatin-induced effect on serum lipemic profile compared to rosuvastatin alone [28].

Taking into account all these issues, we conducted a randomised, controlled, open-label study on patients suffering from ischemic heart disease who had not achieved the therapeutic target with a previous treatment with simvastatin 20 mg/day in order to evaluate the efficacy of the combination therapy of a statin and a nutraceutical. Specifically, the purpose of the study was to assess whether the combination of a nutraceutical (bergamot, phytosterols, artichoke and vitamin C) to simvastatin may result in the achievement of the target range in the absence of side effects. The primary endpoint was to verify the therapeutic efficacy of the combination of simvastatin and the nutraceutical, the secondary endpoint was to evaluate their tolerability.

2. Methods

Sixty-four patients with ischemic heart disease who had not achieved the therapeutic target, under treatment with simvastatin 20 mg, were enrolled.

An informed consent was obtained from each patient according to the European Legislation and the protocol of the study was previously submitted and approved by the Regional Ethical Committee.

In addition, the study protocol was performed according to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected an *a priori* approval by the institution's human research committee.

Patients were randomised 1:1; patients of group A were given simvastatin 40 mg while patients of group B continued their treatment with simvastatin 20 mg adding 2 tablets per day of a nutraceutical composed (per each tablet) of 200 mg of bergamot juice dry extract, 120 mg of phytosterols, 80 mg of artichoke leaf extract, 20 mg of vitamin C.

At enrollment and after 3 months patients underwent a clinical examination and blood tests to measure total cholesterol levels, HDL-c, LDL-c, triglycerides, creatinine, glycemia, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), CPK.

A t-test for paired data was used to compare baseline and post-treatment values for each group.

A chi square test was performed to compare adverse events between groups.

3. Results

Clinical and demographic characteristics between groups are reported in Table 1.

After treatment, patients in group A showed a significant reduction from baseline in total cholesterol, LDL-c and tryglicerides, with a trend towards significance for increase in HDL-c (Table 2). Patients in group B also showed a significant reduction from baseline in total cholesterol, LDL-c and tryglicerides, with a significant increase in HDL-c.

In group A, 4 patients reported myalgia (9,7%) with an increase in CPK, whereas no adverse events occurred in group B ($p < 0.001$). The two groups did not differ for safety parameters, as shown in Table 3.

4. Discussion

The data presented in this study show that the association of the nutraceutical composed of bergamot, artichoke, phytosterols and vitamin C to statin therapy, given orally for 3 months, allows the reduction of daily dose of simvastatin while achieving target lipid values in patients with ischemic heart disease.

In fact, patients taking the nutraceutical composed added to simvastatin showed a reduction of both total cholesterol and LDL-c, of triglycerides and an increase of HDL-c, without side effects.

Considering that side effects typical of statins are dose-dependent, our aim was to demonstrate the efficacy of an alternative therapeutical approach for patients at high cardiovascular risk, without side effects. This may also help improving patient compliance.

The results obtained in the group of the combination therapy are comparable to those obtained with simvastatin at the highest dose (40 mg), thus suggesting an additive effect of the nutraceutical with lower doses of simvastatin.

In addition, the beneficial effects of the combination therapy described in this study were obtained in the absence of side effects typical

Table 1
Characteristics at baseline of each treatment group.

	GROUP A (n = 32) Simvastatin 40 mg	GROUP B (n = 32) Simvastatin 20 mg + Bergamot 400 mg	p
Age	62 ± 15	64 ± 12	ns
M/F	18/14	19/13	ns
BMI	26,4 + ± 2,2	26,1 + ± 2,3	ns
Smoke	11	10	ns
Hypertension	24	22	ns
Diabetes	3	4	ns
Beta blockers	30	31	ns
ACE inhibitors	26	25	ns
ARBs	5	5	ns
Ca antagonists	2	1	ns
Diuretics	1	1	ns
Antiplatelet	32	32	ns

ACE = angiotensin-converting-enzyme; ARBs = angiotensin receptor blockers; BMI = body mass index; Ca = calcium; F = female; M = male; ns = non significant.