IJC Metabolic & Endocrine 11 (2016) 3–6

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

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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ARTICLE INFO

Article history:
Received 22 February 2016
Accepted 7 March 2016
Available online 18 March 2016

Keywords:
hyperlipidemia
simvastatin
nutraceutical
ischemic heart disease
side effects

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

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcme.2016.03.001

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.

Table 2
Comparisons between baseline and post-treatment values within each treatment group.

	GROUP A (n = 32) Simvastatin 40 mg			GROUP B (n = 32) Simvastatin 20 mg + Bergamot 400 mg		
	baseline	3-months	p-value	baseline	3-months	p-value
Total cholesterol (mg/dl)	177 +/-17	162 +/-13	**0.001**	172 +/- 21	151 +/-16	<**0.001**
LDL-c (mg/dl)	107 +/-9	92 +/-5	<**0.001**	103 +/-7	85 +/-5	<**0.001**
HDL-c (mg/dl)	44 +/-5	46 +/-3	*0.05*	41 +/- 4	43 +/-3	**0.023**
Tryglicerides (mg/dl)	131 +/-10	118 +/-8	<**0.001**	139 +/- 13	122 +/-9	<**0.001**

HDL = high density lipoprotein; LDL = low density lipoprotein.

of statin therapy at high dosage, such as myopathy and myalgia, that are a major cause of discontinuation of lipid-lowering therapy [29].

Nevertheless, beyond the clear anti-hyperlipidemic effect of the nutraceutical, the mechanism of action of the single substances remains to be elucidated, as well as the possible synergistic effect of the natural active ingredients within the formulation.

Several studies describe the cholesterol lowering effect of plant sterols and plant stanols, by reducing intestinal absorption of exogenous cholesterol [30].

Some studies have described the hypocholesterolaemic effect of artichoke leaf extract, a natural compound traditionally used for jaundice and liver insufficiency [31]. Quantitative measurements show that artichoke extract inhibits cholesterol biosynthesis in a concentration dependent manner [32].

While some authors suggested cynarine (1.5-di-caffeoyl-D-quinic acid) as the principal active component of artichoke [33], more recent findings indicate a role for the flavonoid luteolin in the inhibiting effects of cholesterol synthesis [34].

With regard to the lipid-lowering effect of bergamot, several studies described the properties of the flavonoids, contained in high amount in this species of the genus Citrus [35].

A major contribution to the hypolipidemic properties of bergamot juice extract seems to be related to the modulatory properties in the flavanone glycoside component, in particular naringin and neo-hesperidin.

In addition to the antioxidant properties of the flavonoids, the effect of both naringin and hesperidin seems also to involve direct inhibition of the HMG-CoA reductase enzyme system [36].

Furthermore, bergamot juice is rich in brutieridin and melitidin, two flavanone derivatives which have been shown to selectively inhibit HMG-CoA reductase [25].

Thus, their hypolipemic properties, mainly due to their content of flavonoids, may explain the above described beneficial effect of the compound of bergamot, artichoke and phytosterols in patients with cardiovascular risk.

5. Study limitations

Some limitations should be taken into account when interpreting our results mentioned above. The main limitation of this study is its single-blind design. In addition, the mechanisms of action of nutraceuticals remain to be elucidated.

Table 3
Safety parameters at baseline and after treatment within each treatment group.

	GROUP A (n = 32) Simvastatin 40 mg			GROUP B (n = 32) Simvastatin 20 mg + Bergamot 400 mg		
	baseline	3-months	p	baseline	3-months	p
GOT	22 ± 4	23 ± 5	ns	21,5 ± 4	23,5 ± 4	ns
GPT	24 ± 3	25 ± 4	ns	25 ± 3	25,5 ± 4	ns
CPK	86 ± 19	87 ± 15	ns	89 ± 13	87 ± 20	ns

CPK = creatine phosphokinase; GPT = Glutamic Pyruvic Transaminase; GOT = Glutamic Ossalacetate Transaminase.

6. Conclusions

Our data show that the combination of a nutraceutical composed to lower dose of simvastatin enhances the effect of the simvastatin alone in normalising serum lipid profile.

Clinically, this may allow a reduction in daily simvastatin doses for reaching and maintaining patients to target levels of cholesterol.

This innovative approach could represent a useful tool in terms of patient compliance to therapy, by reducing the occurrence of disorders due to intolerance to statins. Further studies are needed to clarify the mechanisms of action of nutraceuticals.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest. Costanza Valentina Riccioni is member of Esserre Pharma Srl.

Acknowledgements

This work was supported by project PON03PE-00078_1 (Italian Ministry of Research).

The nutraceutical was provided free by the company Esserre Pharma Srl.

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