Complex α-Lypoic Acid, Ginkgoselect Phytosome and Leucoselect Phytosome in Patients with Chronic Venous Insufficiency of the Lower Limbs: Therapeutic Effectiveness and Impact on Quality of Life

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Abstract

Background: Chronic venous disease (CVD) is a common clinical condition, especially relevant for its impact on public health and its related economic burden. Veno-Active Drugs (VAD) are an heterogeneous group of drugs, widely used in the treatment of CVD. In the last years some food supplements, similar to VAD but with different compounds concentrations raised some confusion in this field. The complex Lypoic acid, Ginkgoselect phytosome and Leucoselect phytosome is a food supplement based on molecules exhibiting different but synergic activities never prospectively tested in patients with CVD.

Methods: Consecutive ambulatory patients with objectively documented CVD and a CEAP "C" up to 5 were eligible for the study. Patients were to take 1 fast-slow tablet of the complex twice-daily for 2 months, followed by 1 fast-slow tablet once-daily for other 4 months, for a total of 6 months. Presence and magnitude of CVD-related signs and symptoms (with "C" of the CEAP classification), evaluation of patients' quality of life (with VEINES-QoL/Sym questionnaire) and assessment of safety and tolerability of the complex at baseline and after 2 and 6 months (with revised Venous Clinical Severity Score, rVCSS) were recorded.

Results: 97 patients enrolled and evaluated. The proportion (65%) of the patients with a rVCSS score>5 at baseline decreased to 35% at 6 months (P <0.001). The number of patients with a scoring of "none" for the item "Pain or other discomfort" increased from 8% at baseline to 54% at 6 months (P=0.001). The pairwise comparison yielded significant results between the 3 time-points for the rVCSS (p<0.00001) and the VEINES-Sym (p<0.00001), while for the VEINES-QoL score between the baseline and the end of the study only (p=0.0016).

Conclusion: The complex Lypoic acid, Ginkgoselect phytosome and Leucoselect phytosome seems beneficial for reducing leg complaints, and effectively improves QoL in patients with CVD.

Keywords: Chronic venous disease; Treatment; Food supplement; Deep-vein thrombosis

Introduction

Chronic venous disease (CVD) is a common clinical condition, especially relevant for its impact on public health and its related economic burden. CVD is a result of venous reflux, venous obstruction or both. This term includes any morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care.

Chronic venous insufficiency (CVI) is a term reserved for advanced CVD, which is applied to functional abnormalities of the venous system producing edema, skin changes, or venous ulcers [1].

CVD denotes a continuum of signs and symptoms, ranging from early asymptomatic minor skin changes, such as telangiectasias and reticular veins, to late major symptomatic complications, such as: chronic pain, significant functional impairment, and at the end stage, venous ulcer.

The prevalence of CVD in the adult population, particularly in developed industrialized and occidental countries, ranges between 10 to 60% in males, and between 50 to 60% in females; being clinically evident in 10-20% and 10-30%, respectively. The observed annual incidence of CVD is 2.6% in women, and 1.9% in men [2]. Pregnancy and number of deliveries have been advocated to explain gender differences, that may be observed up to the 5th-6th decade, but disappear in the elderly; however, the supporting evidence in the literature is sparse. Other potential risk factors, more consistently associated with CVD in clinical trials are: familiarity, obesity (OR 6.5 in men and 3.1 in women with BMI>30), and every day prolonged upright orthostatic position [2-11].

In 1994 an international committee of the American Venous Forum, endorsed by the Society for Vascular Surgery, proposed the CEAP classification, that was since then universally adopted as the standard CVD grading system, having been published in 26 journals

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and books, and translated in nine languages [12]. It was revised in 2004 and currently it is a mainstay for clinical papers reporting on CVD [13]. The CEAP classification takes into account not only the clinical ("C" of CEAP) aspects of CVD, but also its etiological ("E"), anatomical ("A"), and pathophysiological ("P") components, thus enabling a more comprehensive assessment of the severity of this disease [12-14].

In 2002, the American Venous Forum introduced the VCSS (Venous Clinical Severity Score), a highly reproducible score, that was subsequently updated to the currently used version (revised VCSS, rVCSS) [15-17]. The rVCSS, meticulously accounting for any variations of signs and symptoms over time, is typically used to evaluate the outcome of either a surgical procedure or a pharmacological intervention; or the natural history of CVD in untreated patients [10]. The putative pathophysiological mechanism of CVD is a gradual increase of venous hypertension due to valvular incompetence, leading to irreversible modifications of the vessel-wall over time, such as enlargement, winding, and increased wall-permeability. The latter trigger edema and hemosiderin collection, promoting cell-mediated infiltration, inflammation, activation of the macrophages/monocytes system, and expression of adhesion molecules such as ICAM-1, selectine, IL-1 and TNF1 [18].

Both edema and hemosiderin collection are major determinants of disease progression from the clinical point of view, being responsible for the onset of classic symptoms, including pain, heaviness, cramps, itching, and restless-leg syndrome; and signs, including dyschromia, dermatitis and dermal fibrosis, the ultimate step toward the development of venous ulcer [18,19]. Typically, symptoms severity worsens over time, paralleled by increasing CEAP scores; similarly, patients' quality of life becomes less and less satisfying with symptoms progression [20].

Accordingly, a study testing any intervention for treatment of CVD, along with a standardized evaluation of clinical outcomes with the rVCSS and/or the CEAP scores should also include the systematic assessment of the patients' quality of life, and perspective. The latter are currently considered a key point, and should preferably be measured with a validated and reproducible method, such as a general quality of life questionnaire (i.e., SF-36, Nottingham Health Profile, EuroQol), or one specifically validated in patients with CVD (i.e., Venous Insufficiency Epidemiological and Economic Study, VEINES-QOL/Sym; Chronic Venous Insufficiency Questionnaire, CIVIQ) [18-22].

Veno-Active Drugs (VAD) is an heterogeneous group of drugs, some of them of sinthetic origin but the most of them of vegetal origin. Their use is widely accepted and recommended from the International Guidelines, but nevertheless in the last years some food supplement, composed by the same compounds of vegetal origin but in different concentrations as compared to VAD, raised some confusion. Food supplements, unlikely of VAD, did not show to be effective and as a consequence did not attain any marketing authorization from the Italian health authorities. On the other hand, some VAD, such as the Red Grapes Vine leafs extracts (*Vitis vinifera*), are registered as "drug" in seven countries of the European Union (EU) and as "food supplement" in other eight countries. These compounds act on the venous tone, on the inflammatory process of the venous valves and venous wall, and on the wall permeability (edema) with a different level of efficacy in the management of the chronic venous disorders [23].

The complex Lypoic acid, Ginkgoselect phytosome and Leucoselect phytosome [24] is a food supplement based on three active molecules exhibiting different but synergic activities. The lypoic acid is an amphipatic molecule with strong anti-ossidative properties, mainly used in neurologic diseases, thanks to its neurotrophic e neuroprotective properties. It has also proven anti-inflammatory properties, thanks to its ability to reduce the expression of citokynes/chemokines that are typically over-expressed in patients with venous insufficiency, and so its potential effect in CVD patients could be the reduction of the inflammation and of the paraesthesia. The Ginkgoselect phytosome is a selection of bioflavonoids derived from Ginkgo biloba, showing a synergic activity together with the lypoic acid on the reduction of the pro-inflammatory molecules over-expressed in CVD patients. The Leucoselect phytosome is a selection of procianidolic oligomers with a stronger affinity for the glycosaminoglycan-rich vascular structures, such as the venous district. The leucocyanidines adhere to the venous wall with a sticky-effect producing anti-oxidative (with a synergic activity together with lypoic acid) and vasoprotective actions thanks to an anti-enzymatic activity, inhibiting elastase, collagenase and ialuronidase.

Aim of this study was to evaluate if the complex Lypoic acid, Ginkgoselect phytosome and Leucoselect phytosome improves the symptoms and the quality of life over time of patients with CVD of the lower limbs

Methods

This was a multicenter, prospective cohort, observational, pilot study. The study was conducted according to principles contained in the Declaration of Helsinki. Being an observational study only, the approval of the Institutional Review Board of each centre was not requested and necessary prior to data collection. Anyway, all considered patients were invited to subscribe a written informed consent before the inclusion in the study.

Patients eligibility

Consecutive ambulatory patients aged>18 years, with superficial venous reflux objectively documented by color-coded Doppler ultrasound and a CEAP "C" up to 5, were eligible for the study; provided they did not receive any venoactive treatment in the 15 days preceding enrolment in the study.

Exclusion criteria

- Unable to provide informed consent.
- Pregnancy, and breastfeeding.
- Severe disability, or prolonged immobilization.
- Active venous ulcer (CEAP "C"=6).
- Included in other clinical trials in the last 3 months.
- History of, or acute venous thromboembolism, including superficial vein thrombosis.
- Post-thrombotic syndrome with Villalta score>4.
- Objectively documented deep-veins reflux.
- Chronic lymphedema of the lower limbs.
- Renal (creatinine clearance <30 mL/min), hepatic (AST, ALT>3 UNL), or cardiac failure (NYHA III-IV).
- Objectively documented active cancer.
- Life expectancy<6 months.
- Recent (<3 months), or planned surgery for varicose veins or PTCA.

- Known thrombophilia.
- Malnutrition or malabsorption.
- Ostheo-articular, cutaneous, muscular, or ischemic pain of the lower limbs, either acute or chronic.
- Chronic use of NSAIDs, corticosteroids, immunosuppressive drugs, diuretics, analgesics.
- Alcohol or drug abuse.
- Diabetes.
- Uncontrolled arterial hypertension.
- Peripheral arterial disease with ABI <0.9.
- Severe rheumatologic disease.

Evaluation of effectiveness

- Variation of the rVCSS score, at 2 and 6 months from baseline.
- Variation of patient quality of life and complaints, as assessed by the VEINES-QoL/Sym questionnaire, at 2 and 6 months from baseline.

Evaluation of safety

- Tolerability of the food supplement.

Regimen

Included patients were to take 1 fast-slow tablet of the complex Lypoic acid, Ginkgoselect phytosome e Leucoselect phytosome (Blunorm Forte®, Laborest S.p.A., Nerviano, Italy) twice-daily for 2 months, followed by 1 fast-slow tablet once-daily for other 4 months, for a total of 6 months.

Baseline and outcome assessment

We systematically recorded the presence and magnitude of CVD-related signs and symptoms, evaluated the patients' quality of life, and assessed the safety and tolerability of the complex, at baseline and after 2 and 6 months. Specifically, to quantify the patients' complaints we calculated the "C" score of the CEAP, the rVCSS score and measured the circumference of the legs. To appraise the patients' quality of life, we used the VEINES-QoL/Sym questionnaire.

In case of suspected superficial and/or deep-vein thrombosis, or of pulmonary embolism, patients underwent color-coded Doppler ultrasound, chest CT-angiography, or both, as appropriated.

Statistical analysis

The analysis was conducted on the intention-to-treat (ITT) population, including all patients receiving at least one dose of the product. For the efficacy analysis, patients were considered on the basis of the time elapsed from the beginning of the treatment (2, 6 months). Significance level was set at 0.05 (two-sided).

Treatment compliance was assessed at the end of the study and was defined as follows: compliance=100 × total number of tablets effectively taken/total number of tablets scheduled.

Sample size: We hypothesized that the rVCSS score at the beginning of the treatment would be>5 points in 60% and <=5 points in 40% of patients, respectively; the respective proportions being 80% and 20% after 6 months of treatment. Based on these assumptions, choosing an

alfa significance level of 0.05, a sample size of 93 patients has a power of 85%, using the McNemar test for matched data.

Data analysis: The proportions of patients with an rVCSS score ≤5 points or >5 points, recorded at baseline and at the end of the treatment, were compared using the McNemar test for matched data. The raw scores for the quality of life (VEINES-QoL score) and subjective symptomatologic evaluation (VEINES-Sym score), recorded at baseline, and after 2 and 6 months, were first transformed to z-score equivalents (mean, 0; standard deviation, 1), and then converted to T-scores (mean, 50; standard deviation, 10), in order to provide an easily understandable range of scores, as usual [15]. Afterwards, the VEINES-QoL score and the VEINES-Sym score were separately analyzed by the "Repeated Measures Analysis of Variance", to estimate variations of within-subject T-score. The Greenhouse-Geisser adjustment was applied to degrees of freedom, and equal weights were attributed to measurements. The Bonferroni correction was used for pairwise planned comparisons between the 3-time points (0, 2 and 6 months). Analogue analyses was performed for rVCSS raw values. A standard synthesis of safety data and of adverse events was also provided.

Results

We enrolled and evaluated 97 subjects in 3 clinical centers. Table 1 shows the main characteristics of patients. Patients were generally middle-aged females, moderately over-weight, but with a normal blood pressure, and heart rate. Treatment compliance was high, being ≥ 80% for 90% of patients.

Data concerning the evaluation of effectiveness is reported in Table 2. Shortly, we were able to observe statistically significant and clinically favorable modifications of the rVCSS, the VEINES-QoL score, and the VEINES-Sym. The rVCSS score showed the greatest advantageous variations during the study period. In particular, as shown in Table 3, the proportion (65%) of the patients who had a score >5 at baseline, was almost halved (35%) at 6 months (P <0.001, McNemar test for matched

Feature	Data
Gender, female (*)	84 (85.7%)
Age, years	52.6 ± 11.3
Weight, Kg	71.3 ± 18.7
BMI	25.5 ± 5.2
Systolic blood pressure, mmHg	122.3 ± 14.2
Diastolic blood pressure, mmHg	76.6 ± 10.8
Hearth rate, beats/min	72.3 ± 8.4

Table 1: Characteristics of the 97 included patients at baseline. Data expressed as mean ± standard deviation, except (*) expressed as number (%).

Item	Baseline	2-month	6-month	P
Right leg circumference, cm	32.5 ± 8.2	32.5 ± 8.1	32.3 ± 9.7	ns
Left leg circumference, cm	32.5 ± 8.3	32.4 ± 7.9	32.3 ± 9.7	ns
CEAP "C" score	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	ns
rVCSS score	5.9 ± 3.7	4.7 ± 3.1	4.2 ± 3.3	<0.00001
VEINES QoL score	48.1 ± 10.7	50.3 ± 10.4	51.6 ± 8.9	<0.003
VEINES Sym score	40.7 ± 12.3	53.0 ± 8.8	56.3 ± 8.9	<0.00001

Table 2: Evaluation of the effectiveness of Blunorm Forte. Data expressed as mean ± standard deviation.

	rVCSS score	
	≤ 5	>5
Baseline	34 (35)	63 (65)
6 months	63 (65)	34 (35)

Table 3: Modification of the rVCSS score at the end of the study. Data expressed as number (%).

data). In particular, the number of subjects with a scoring of "none" for the item "Pain or other discomfort" increased from 8% at baseline to 54% at 6 months (P=0.001). Of note, only 1 patient worsened, switching from a score of ≤ 5 at baseline to >5 at 6 months.

The within-subject time-course analysis for the rVCSS, the VEINES-Qol, and the VEINES-Sym score is displayed in Figures 1-3, respectively. Significant and favorable differences between the baseline assessment and the evaluation at 2 and 6 months were observed for all the scores. The pairwise comparison yielded significant results between the 3 time-points for the rVCSS ($p < 0.00001$) and the VEINES-Sym ($p < 0.00001$), while for the VEINES-QoL score between the baseline and the end of the study only ($p=0.0016$).

Conversely, we could not detect any changes in terms of both the leg circumference and CEAP "C" score.

As to the safety evaluation, during the study period we observed 6 (6.1%) transient mild adverse events, as follows: 2 rashes, and 4

Figure 1: Within-subject time-course of the rVCSS score, as estimated by repeated measures ANOVA. Circles represent means, and vertical bars denote 95% confidence limits.

Figure 2: Within-subject time-course of the VEINES-Qol score, as estimated by repeated measures ANOVA. Circles represent means, and vertical bars denote 95% confidence limits.
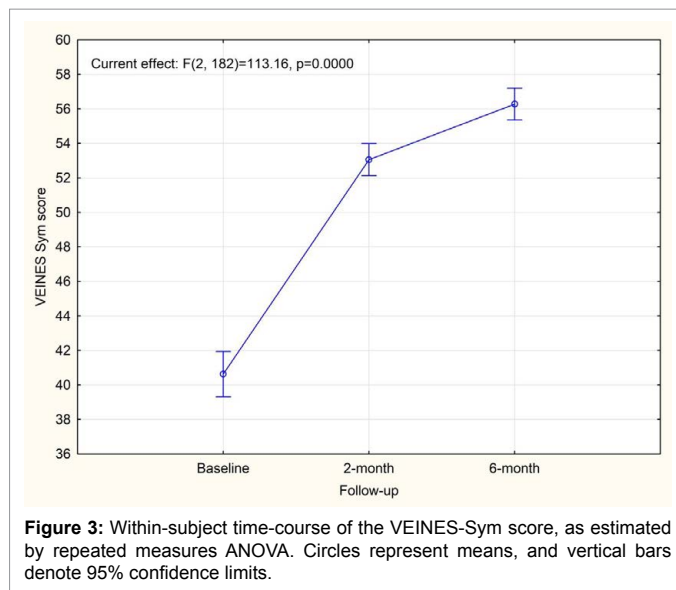

Figure 3: Within-subject time-course of the VEINES-Sym score, as estimated by repeated measures ANOVA. Circles represent means, and vertical bars denote 95% confidence limits.
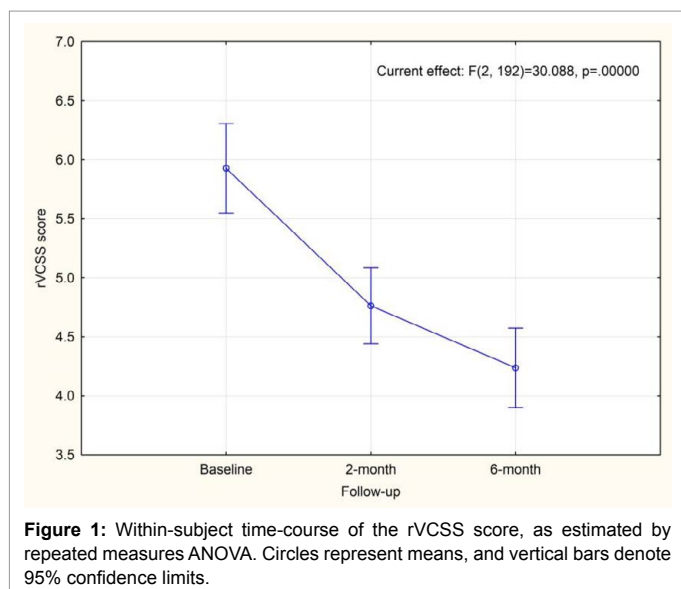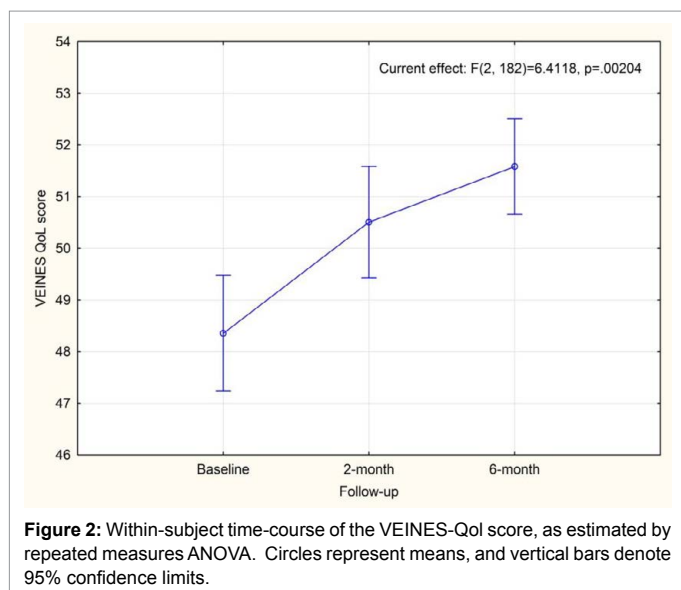
epigastric pains. All events resolved with only a temporary interruption (4-5 days) of the food supplement. There were instead 3 (3.1%) complete withdrawals related to poor general compliance.

Discussion

This is only an exploratory, observational pilot study and to our knowledge, this is the first prospective observation investigating the effectiveness of the complex Lypoic acid, Ginkgoselect phytosome and Leucoselect phytosome in patients with CVD. After 6 months of intake, the complex significantly improved patients' symptoms, as well as quality of life. At the same time, the supplement was generally safe, well tolerated, and fairly accepted, as reflected by the high compliance rate at 6 months.

The beneficial effects of the complex on symptoms are possibly due to its anti-inflammatory and anti-oxidant properties, as already described by some previous reports of the literature. Costanzo et al., in a small, open study of 30 consecutive patients with CVD receiving either one tablet of the complex, or matching placebo daily for 4 weeks, observed a significant reduction of the rVCSS score in the intervention group, as compared to the control group [25]. We also recorded a similar statistically significant reduction of the rVCSS score in our patients, although the magnitude of the effect was larger in our cohort, probably due to the different intake regimen (one versus two tablets daily), and to the more advanced disease in our patients, as reflected by both a higher baseline CEAP "C" score, and a mean baseline rVCSS score (C0-C5 vs. C0-C3; and 5.9 ± 3.7 vs. 2.7 ± 0.95, respectively).

As shown in Figures 1-3, the benefits of the supplement are more evident during the first 2 months (twice-daily administration), than in the following 4 months (once-daily administration).

Conversely, we were not able to observe significant changes in terms of both leg circumference and CEAP "C" score. While the CEAP finding was expected, being based on objective findings due to the effects of chronic venous disease, thus, not likely to be significantly modified by treatment, the lack of modifications of leg circumference deserves some considerations. We speculate that the anti-inflammatory effect of the complex takes place earlier than its anti-edemigen power. This in turn could justify our findings, as regard to the significant

decrease of symptoms in our patients, not paralleled by a simultaneous significant reduction of leg circumference/edema.

We are aware that our study presents some limitations; in particular: the relatively small sample size, the absence of a control group and of blinded randomization, and the mostly mild disease stage (CEAP C0-C2) of included patients; anyway, this was only an observational pilot study aiming to test the clinical effectiveness of the complex and its impact on the symptoms and on the quality of life in patients with CVD and preliminarily performed in order to obtain some data suitable to design a bigger randomized clinical trial. Moreover, at this moment, being a pilot study, we had not resources enough to perform a larger investigation with a control group and to provide a blinded randomization.

In conclusion, the complex Lypoic acid, Ginkgoselect phytosome e Leucoselect phytosome may be beneficial for reducing leg complaints, and effectively improves quality of life, in patients with mild CVD. A larger study, enrolling patients with a broader spectrum of CVD, possibly with a randomized, placebo-controlled design, would be desirable to better define the effectiveness of the complex.

Acknowledgement

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