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Original article

L-cysteine and zinc L-carnosine in the therapy of chronic atrophic gastritis: Clinical efficacy and tolerability

Maria Piera Panozzo[1], Stefano Rossi[2], Marilisa Franceschi[3], Alessandra Violi[3], Antonio Ferronato[3], Kryssia Isabel Rodriguez Castro[3], Lorenzo Brozzi[3], Lorella Franzoni[4], Francesco Di Mario[4], Pellegrino Crafa[4]

[1]Department of Laboratory Medicine, ULSS7 Pedemontana, Alto Vicentino Hospital, Santorso (VI), Italy; [2]Department of Pharmacology, University of Ferrara, Italy; [3]Endoscopy Unit, Department of Medicine, ULSS7 Pedemontana, Alto Vicentino Hospital, Santorso (VI), Italy; [4]Department of Medicine and Surgery, University of Parma, Italy

Abstract. *Background and aim:* Chronic atrophic gastritis (CAG) is characterized by gastric atrophy due to loss of the mucosa cells. Clinical manifestations are represented by gastrointestinal symptoms and/or alterations due to macronutrient deficiency. There is no specific therapy for CAG although some medical devices appear promising: L-cysteine reduces acetaldehyde levels in the stomach, zinc L-carnosine shows direct cytoprotective and anti-inflammatory action. We evaluated in CAG patients the therapeutic efficacy and tolerability of both devices on the improvement of gastric functional picture and symptoms as compared to a control group. *Methods:* 200 CAG patients were recruited and divided into: Group 1: L-cysteine 300 mg/daily; Group 2: zinc L-carnosine 75 mg/daily; Group 3: control group without any therapy. Patients were followed up for three months to evaluate the efficacy of both molecules and the possible appearance of side effects and adverse events. *Results:* Increased pepsinogen I (efficacy rate 37.1% and 21.3%) and decreased gastrin 17 serum levels (efficacy rate 41.3% and 58.7%) were found for L-cysteine and zinc L-carnosine, respectively. An improvement or no appearance of new symptoms was detected (65.7% for L-cysteine and 77.3% for zinc L-carnosine). Both devices appeared well tolerated (compliance rate of 100% for L-cysteine and 93.7% for zinc L-carnosine) and side effects were limited to manifestations that resolved after stopping therapy. *Conclusions:* The clinical efficacy of both molecules on CAG patient management represents a promising result; however, further randomized prospective studies performed on larger series for a prolonged time and on individual pathology groups are mandatory to confirm these data. (www.actabiomedica.it)

Key words: chronic atrophic gastritis, L-cysteine, zinc-L-carnosine, pepsinogen I, gastrin 17, OLGA

Introduction

Chronic gastritis (CG) represents a clinical condition induced by a persistent inflammatory state of the gastric mucosa (1-4); it frequently may evolve into chronic atrophic gastritis (CAG) due to loss of the cellular component (5-7). Only in recent decades has the interest of the scientific community in this condition increased considering its characteristics of a precancerous condition (8-10). Epidemiological data on CAG are rather not always easy to compare due to the different methodological approaches used (11-18).

Currently, three forms of CAG are known: autoimmune (A-CAG), related to Helicobacter pylori infection (Hp-CAG), and mixed. They differ based on etiological agent, anatomical localization and extent of atrophy. A-CAG is mainly characterized by atrophy of the body fundus, severe impairment of gastric secretion and impaired absorption of vitamin B12 (19-27). From a clinical point of view, A-CAG is often

accompanied by pernicious anemia caused by a lack of vitamin B12 absorption from intestinal mucosa, or microcytic anemia due to iron deficiency (28-36). Unlike A-CAG, Hp-CAG is triggered by an infectious condition that initially develops atrophy in the antrum (37); however, as the infection evolves, it can spread, resulting in multifocal atrophy.

Finally, in the mixed form the effects of the autoimmune response are added to those of the infectious condition which probably represents the initial cause of the phlogistic process (38-39). The dual cell damage induced by infection and autoimmunity results in pangastritis which affects both the antral and the body-fund areas (40).

The different pathogenetic pathways may determine the onset of various clinical pictures with gastrointestinal (up to 50-60% of CAG patients) and extra-gastrointestinal manifestations (41) due to loss of parietal cells in the oxyntic glands and consequent hypo/achlorhydria. Dyspepsia (epigastric pain, heartburn) is the most common clinical symptom and, in 80% of cases, is associated with reduced gastric emptying (42-43). Acid regurgitation and early satiety, nausea, bloating, diarrhea, and abdominal pain may also be present. As regards A-CAG, two papers report the presence of epigastric pain, early satiety and/or postprandial fullness with a frequency of 35.5%, 10.0% and/or 7.0%, respectively; reflux-like symptoms, such as heartburn and acid regurgitation, are described in 24.2% and 12.1% of cases, respectively (7-44).

The measurements of serum pepsinogen I (PGI), pepsinogen II (PGII) and gastrin G17 (G17) are helpful for early identifying a functional mucosa alteration (45-52), particularly in those subjects in which a gastric disorder can arise even before the appearance of the symptoms themselves (53).

To complete the bio-humoral investigation, other serological markers, such as vitamin B12, folate, chromogranin (a predictive marker for the development of carcinoid) and homocysteine (an indicator of malabsorption of vitamin B12 for hypo/achlorhydria) must be investigated (54-59); finally, the evaluation of parietal cell and intrinsic factor antibodies or Hp antibodies allows to define the type of CAG, autoimmune or infectious (60).

To date, there is no pharmacological treatment for CAG resolution, nor for its regression. The only approach is represented by a correct follow-up and the implementation of strategies able to prevent or slow down its progression and alleviate symptoms.

Taking into account that CAG often does not present dyspeptic symptoms, but only micronutrient deficits or hematological alterations, the main treatment in patients with A-CAG remains to prevent and limit the onset of such deficiencies (61-66).

Recently, some therapeutic options have been considered to reduce gastric inflammation and prevent atrophy progression, but results are often conflicting (67); the evidence is moderate-low and very few studies exploring the effectiveness of these medical devices in an atrophic context are available (61). Some agents may be useful based on their detoxifying, antioxidant, anti-inflammatory and repair properties against gastric mucosal damage. Among them, two molecules, L-cysteine and zinc L-carnosine, could play a role in the therapy of CAG: the first lowers acetaldehyde levels in the stomach reducing symptoms and stabilizing atrophy (68-69) and the last one shows direct cytoprotective and anti-inflammatory action through an antioxidant effect and modulation of cytokines (70-72). If rare clinical studies on the effect of L-cysteine in CAG are present in literature, there is no scientific production on the role of zinc L-carnosine in gastric corpus-fundus atrophy; no clinical study has compared, for the first time, the effects of both molecules in the treatment of CAG.

The present work, therefore, was performed to evaluate:

1. the short-medium term therapeutic efficacy of L-cysteine and zinc L-carnosine on improving the gastric functional picture and symptoms in patients affected by CAG, either of autoimmune or mixed origin, compared to a control group not undergoing therapy;
2. the tolerability of the two medical devices.

Patients and methods

This prospective controlled study was conducted at the Digestive Endoscopy Unit – ULSS7 Pedemontana, Alto Vicentino Hospital, Santorso

(VI) - according to the Helsinki Declaration and approved by the local Ethics Committee (Identifier: 92687, approved 03/02/2021); all patients filled and signed the informed consent.

Population

From 2015 to 2023, 718 patients (257 males and 461 females, mean age 66.2 ± 14.3 years, age range 16-93) came to the Digestive Endoscopy Unit observation and clinically classified for the presence of body-fundus CAG.

Between December 2022 and May 2023, during the usual follow-up controls, a subgroup of this cohort constituted by 200 CAG patients (65 males and 135 females, mean age 63.2 ± 13.6 years, age range 22-88) was prospectively enrolled for this study.

We considered the following inclusion criteria: 18<age<90 years, presence of CAG confirmed on endoscopic (corpus-fundus atrophy), histological and serological findings, negative Hp infection for at least one year. Exclusion criteria were: lack of informed consent, diagnosis of CAG not supported by serological gastric function test, presence of CAG only in the antrum, previous surgery on the upper gastrointestinal tract or previous history of neoplasms, therapy with pump proton inhibitors.

Treatments

The study was designed as described in Figure 1.

At the first control visit (time T0) demographic, lifestyle (diet, smoking, alcohol) data and predisposing (family history, pathologies related to CAG) factors, pharmacological history and symptoms were recorded. In addition, hematochemical (blood count, ferritin, vitamin B12, folic acid, homocysteine, chromogranin) and gastric function parameters (PGI, PGII, G17, IgG Hp antibodies), were evaluated together with the results of endoscopic and histological procedures which were carried out according to the Sydney System Guidelines (73) and OLGA staging criteria (74-76), respectively.

Finally, patients were subdivided into three groups depending on the type of therapy administered:

- Group 1: 70 patients (21 males and 49 females, mean age 64.2 ± 12.5 years, age range 36-85) were treated with L-cysteine (Acetium®, Biohit Oyj, Helsinki, Finland) 100 mg x 3/day orally before meals (77);
- Group 2: 80 patients (27 males and 53 females, mean age 62.6 ± 14.3 years, age range 22-84) received zinc L-carnosine (Hepilor®, Italian Pharmaceutical Company, Sant'Egidio alla Vibrata, Teramo, Italy) 37.5 mg x 2/day orally (10 a.m. and 10 p.m.) maintaining an hour of fasting after hiring;
- Group 3: 50 patients (17 males and 33 females, mean age 62.6 ± 12.7 years, age range 30-88) did not have therapy, but were monitored in follow-up.

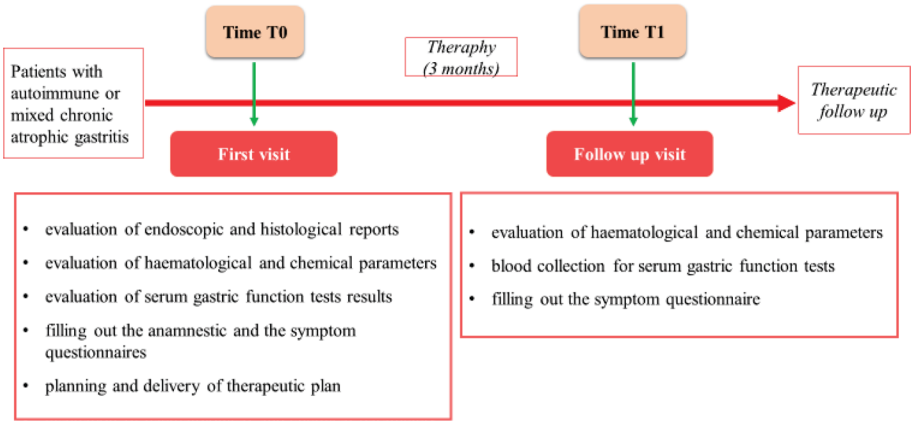

Figure 1. Study design.

All subjects were followed for three months. During treatment, they were examined to record the possible appearance of side effects; compliance was considered good when more than 90% of L-cysteine or zinc L-carnosine tablets were taken by patients. Adverse events were investigated to evaluate the causal relationship with drugs.

Before starting therapy (T0) and at the end of the study (T1) all selected CAG patients were submitted to a symptom questionnaire (modified UGISQUE) (78) aimed to describe the presence, the type, the entity and the variations of symptoms during the observational period (Table S1).

The questionnaire included 15 items for the description of symptoms divided into five symptoms clusters: pain, reflux, maldigestion, non-specific symptoms and extra-digestive symptoms.

It was defined a-symptomatic the patient without any symptom; symptomatic was the patient who reported discomfort in at least one of the considered items. Symptomatology was classified as mild, moderate or severe in relation to the value assigned by a scoring scale (from 0 to 10) (Table S1).

Gastric function evaluation

At time T1, patients underwent a venous blood sample for the second serological evaluation of gastric function parameters. After blood coagulation, samples were centrifuged at 2000 g for 15 minutes and sera were submitted to PGI, PGII, G17 and IgG Hp assays using chemiluminescent immunoassay (CLIA) methods (Maglumi, Shenzhen New Industries Biomedical Engineering Co., SNIBE, Shenzhen, China). To discriminate between the gastric normal function from an atrophic condition, we applied the diagnostic algorithm for CAG: PGI <70 ng/mL and PGI/PGII<3 ratio (79).

Therapeutic efficacy of L-cysteine and zinc L-carnosine

Evaluation of the therapeutic efficacy was performed considering the variations in serum PGI and G17 and in clinical symptoms at time T1 compared to time T0. To allow the measurement of the analyzed data, intervals were defined as indicated in Table 1.

Therapeutic efficacy rates were estimated using equation [1]:

$$[1]\ \text{Effective rate} = \frac{\begin{array}{c}\text{N. markedly}\\ \text{effective cases +}\\ \text{N. effective cases}\end{array}}{\begin{array}{c}\text{Total N. cases}\\ \text{in the group}\end{array}} \times 100\% \ (80)$$

Statistics

All data were automatically stored in an internal database and statistically processed with the SPSS statistical software program for Windows (version 20.1, SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation (SD) and qualitative parameters as a percentual frequency of the total. In the case of normal distribution of data, the evaluation of differences between groups was performed using one-way analysis of variance (ANOVA); the Kruskall-Wallis test was considered in case of negative normal distribution of the data. The study of differences between dichotomous qualitative groups and variables was carried out using the Pearson and Wilcoxon Chi-square test for paired data. All p values were two-tailed with statistical significance at p-value <0.05.

Table 1. Indicators and ranges used to evaluate the effectiveness of both medical devices L-cysteine and zinc L-carnosine. Abbreviations: PGI: pepsinogen I; G17: gastrin 17

Indicators	Ineffectiveness range	Effectiveness range	High effectiveness range
Serum PGI increase	<30%	30-69%	70%-100%
Serum G17 decrease	<30%	30-69%	70%-100%
Symptoms variations	Unvaried or worsened symptoms	No pre- and post-therapy symptoms	Improved symptoms

Results

Population

Demographic characteristics of the three groups of patients are described in Table 2; no statistically significant differences were detected with regards to gender, mean age, body max index, smoking and alcohol intake.

The results of the questionnaire proposed to patients at time T0, which allowed to collect data on symptoms are shown in Table 3.

Table 2. Demographic variables of the studied population subdivided into the three groups of patients. Abbreviations: M: males; F: females; BMI: body max index

	Group 1 L-cysteine (n = 70)	**Group 2 zinc L-carnosine (n = 80)**	**Group 3 No therapy (n = 50)**	**p**
Gender, M/F	21 / 49 (30%,70%)	27/53 (34%, 66%)	17/33 (34%, 66%)	0.857
Mean age (mean±SD)	64.2±12.5	62.6±14.3	62.6 ± 12.7	0.730
BMI (mean±SD)	24.2±3.7	24.9±4.2	24.5±4.3	0.691
Smooking intake (%)				
No	71.4	76.6	70.2	0.863
Yes	2.9	5.2	8.5	
Ex-smokers	25.7	18.2	21.3	
Alcohol intake (%)				
No	41.4	38.5	51.1	0.578
Yes	17.2	47.4	36.2	
Occasional	41.4	14.1	12.7	

Table 3. Symptoms, type of anemia (%) and hematological-chemical data (means±SD) in patients subdivided into the three groups at time T0. Abbreviation: MCV: mean corpuscular volume

	Group 1 L-cysteine (n = 70)	**Group 2 zinc L-carnosine (n = 80)**	**Group 3 No therapy (n = 50)**	**p**
No symptoms (%)	28.6	31.3	16.0	0.152
Symptoms (%)	18.6	26.3	18.0	
Pain	10.0	1.3	8.0	
Reflux	14.3	16.1	24.0	
Maldigestion	21.4	15.0	28.0	
Non-specific symptoms	7.1	10.0	6.0	
Extra-digestive				
Anemia %	54.3	52.6	52.0	0.973
Macrocytic	20.0	21.3	20.0	
Normocytic	15.7	16.3	18.0	
Microcytic	18.6	15.0	14.0	
Hematological-chemical data				
Hemoglobin (g/L)	116.9±25.2	125.0±23.8	123.6±24.5	0.161
MCV (fL)	93.0±14.4	93.8±14.6	92.1±13.0	0.808
Platelets (10^9/L)	235.2±93.6	245.1±75.6	252.8±121.1	0.550
Ferritin (ng/mL)	35.2±56.4	26.5±39.6	38.8±56.8	0.517
Vitamin B12 (pg/mL)	266.7±128.6	255.8±117.0	248.0±110.8	0.879
Folic acid (ng/mL)	10.2±4.7	13.6±6.7	11.0±5.9	**0.012**
Homocysteine (µmol/L)	19.5±19.8	17.3±13.5	20.1±17.8	0.932
Chromogranin (µg/L)	170.5±128.6	191.5±145.0	250.3±185.2	**0.050**

At the beginning of the therapeutic protocol, a part of the patients did not show any symptoms. The remaining part reported the presence of pain, reflux, maldigestion, extra-digestive and non-specific (anemia, asthenia, weight loss and dysphagia) symptoms. Since more than half of the subjects showed signs of anemia, this variable was further evaluated by differentiating it in macrocytic, normocytic and microcytic anemia. The three groups resulted homogeneous (p=0.973) for this parameter.

Table 3 also reports the mean values of hematological and chemical data in the groups considered at time T0. No statistically significant differences were found between the three cohorts except folic acid (p=0.012) and chromogranin (p=0.050).

Considering patients overall, histological results indicated that the majority of them were classified in OLGA II (66.5%) and III (23.0%) stages, while a smaller number of subjects were in stages I (7.5%) and IV (3.0%).

Table 4 shows the subdivision of OLGA stages and subclasses in the three studied groups. The presence of structural damage extended not only in the body (C) but also in the antrum (A) was suggestive for a greater extent of the atrophic damage histologically classified as stage IV.

As regards the type of atrophy, the distribution of patients affected by A-CAG and mixed form (A-CAG and Hp-CAG) is reported. No statistically significant differences were observed for the type of gastritis in the three groups (p=0.612).

Gastric function evaluation

At time T0 all patients underwent the determination of serum gastric function parameters (PGI, PGII, G17 and IgG Hp). The results and the statistical analysis are described in Table 5.

Group 1 showed lower PGI values than the other groups; Group 2 showed higher G17 values even if the differences were not significant. As the severity of the atrophic condition increased, a progressive reduction in serum PGI levels (a) and an increase in circulating G17 levels (b) were observed (Figure 2).

Table 4. Statistical analysis on OLGA histological stages and subclasses in the three groups of studied patients. Abbreviations: OLGA: Operative Link for Gastritis Assessment; A: antrum; C: corpus; CAG: chronic atrophic gastritis; A-CAG: autoimmune chronic atrophic gastritis; Hp-CAG: Helicobacter pylori chronic atrophic gastritis

OLGA staging (%)	**Group 1 L-cysteine (n = 70)**	**Group 2 zinc L-carnosine (n = 80)**	**Group 3 No therapy (n = 50)**	**p**
I	8.6	2.6	12.0	0.716
II	64.2	71.1	66.0	
III	24.3	22.4	20.0	
IV	2.9	3.9	2.0	
A0C1	5.7	2.5	10.0	
A0C2	17.1	18.8	10.0	
A0C3	38.6	47.5	48.0	
A1C1	1.4	1.3	2.0	
A1C2	11.4	2.5	8.0	
A1C3	22.9	21.3	16.0	
A2C2	0.0	2.5	4.0	
A2C3	1.4	1.3	0.0	
A3C2	1.4	1.3	0.0	
A3C3	0.0	1.3	2.0	
Type of CAG (%)				
A-CAG	58.6	2.5	50.0	0.612
Mixed (A- and Hp-CAG)	41.4	47.5	50.0	

Table 5. Serum values (espressed as mean±SD) of gastric function markers in the three groups of studied patients at time T0. The statistical analysis is reported. Abbreviations: PGI: pepsinogen I; PGII: pepsinogen II; G17: gastrin 17; IgG Hp: IgG antibodies to Helicobacter pylori

Time T0	Group 1 L-cysteine (n = 70)	Group 2 zinc L-carnosine (n = 80)	Group 3 No therapy (n = 50)	p
PGI (ng/mL)	9.9±1.3	12.6±1.0	12.8±1.3	**0.005**
PGII (ng/mL)	8.2±0.5	10.2±0.5	9.9±0.7	**0.001**
PGI/PGII	1.2±0.1	1.3±0.2	1.5±0.2	0.297
G17 (pmol/L)	161.9±14.7	241.9±17.8	121.0±15.4	0.297
IgG Hp (EIU)	14.8±1.4	9.3±2.7	22.5±5.3	**0.001**

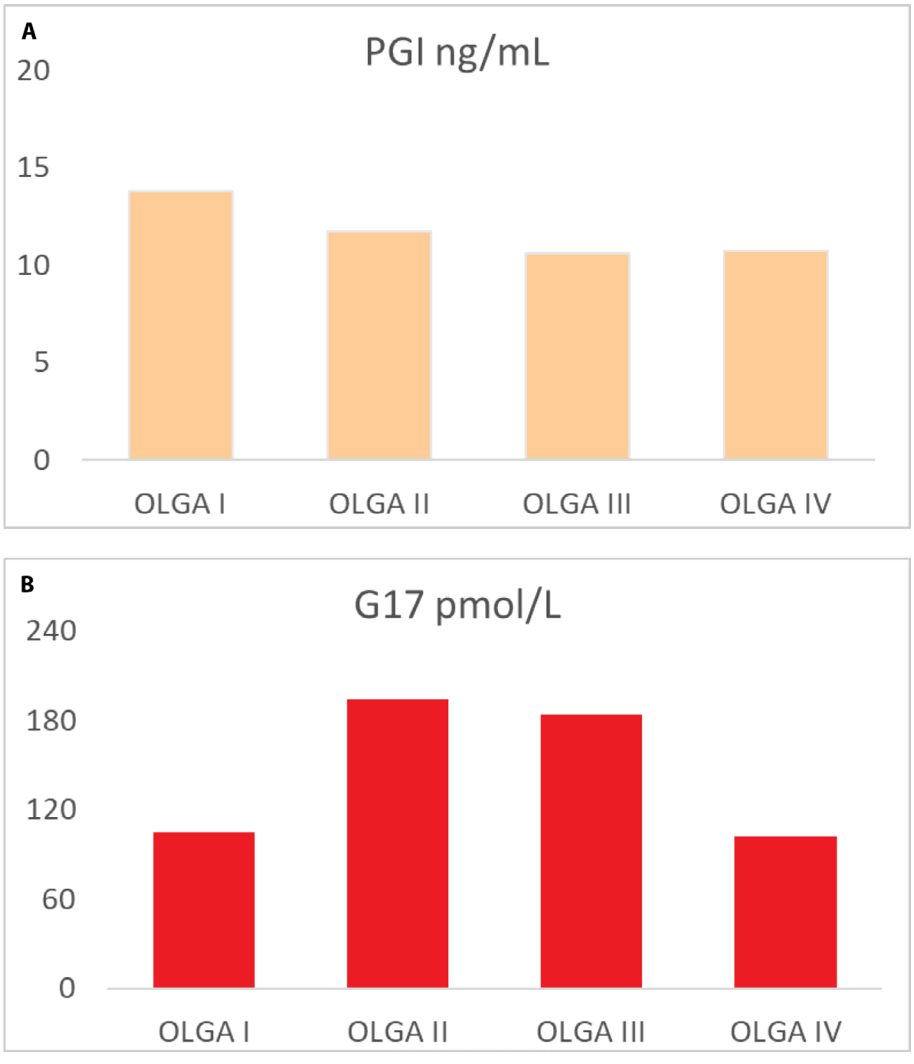

Figure 2. Mean values of pepsinogen I (a) and gastrin 17 (b) related to different histological OLGA stages. Abbreviations: PGI: pepsinogen I; G17: gastrin 17; OLGA: Operative Link for Gastritis Assessment.

However, in the more advanced OLGA IV stage (A2C3, A3C2 and A3C3), a reversal trend was described with stabilization of PGI and reduction of G17 values.

Focusing attention on PGI and G17 changes from T0 to T1, we observed an increase in circulating levels of PGI in both groups treated with L-cysteine and zinc L-carnosine, but not in the control group 3 (Figure 3a).

Patients treated with L-cysteine had a lower baseline PGI value than those in the other two cohorts, signifying a worse initial functional condition; however, the recovery in PGI rate after treatment was better (p=0.019) (Figure 3, a). At the same time, in the zinc L-carnosine subset, significant reductions in G17 were observed for patients in Groups 1 and 2 with a more important trend; vice versa, Group 3 showed a significant increase in serum G17 levels compared to the T0 values, suggesting a worsening functional picture due to the absence of any type of therapy (Figure 3, b).

Therapeutic efficacy of L-cysteine and zinc L-carnosine

In general, compliance towards both medical devices were good with adherence to the therapeutic protocol in almost all subjects. 100% of L-cysteine patients completed the therapy cycle. In the group treated with zinc L-carnosine, however, 5 dropouts occurred (6.25% compared to the total group), 3 due to lack of compliance and 2 due to the appearance of side effects.

To estimate therapeutic efficacy, the increase in serum PGI levels and the decrease in circulating G17 values were taken into consideration. Using the effectiveness ranges reported in Table 1, it was possible to classify the therapy outcome as ineffective, effective, or markedly effective.

In the same way, changes in symptoms were differentiated into unvaried/worsening symptoms, maintained no symptoms and improved symptoms.

Table 6 shows absolute values and relative percentages of patients subdivided, into each group, based on response to therapy.

The percentage effectiveness rates, obtained using equation [1], are shown in Figure 4.

L-cysteine was effective with an overall rate of 37.1% for PGI and 41.3% for the G17; the best efficacy rate was, however, highlighted on the symptoms with an improvement or no appearance of new symptoms during the observation period (65.7%).

The effectiveness of zinc L-carnosine was less evident than that of L-cysteine for PGI (21.3%), but more marked for G17 (58.7%). An improvement in symptoms or no new symptoms onset was detected (77.3%).

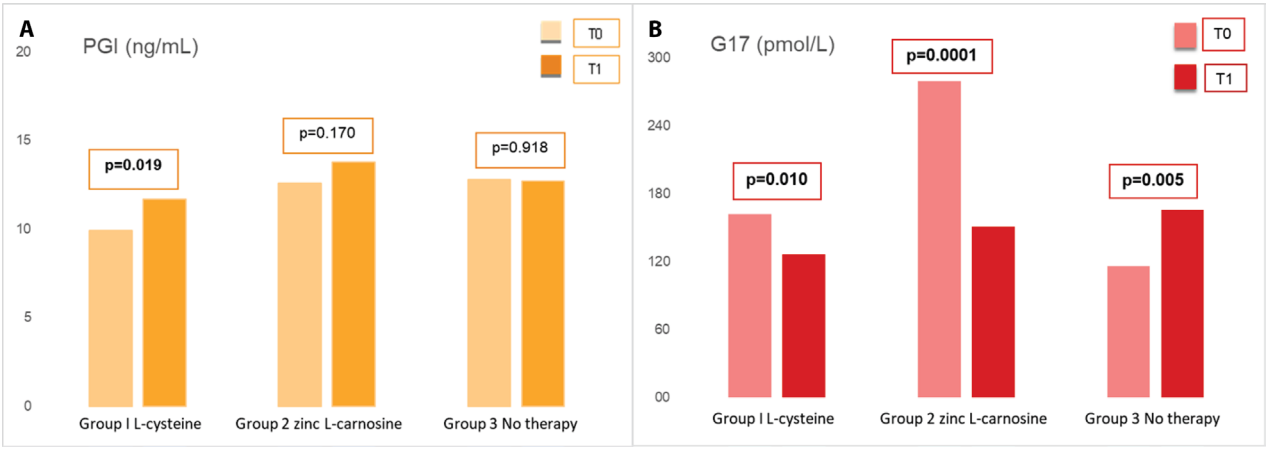

Figure 3. Pepsinogen I (a) and gastrin 17 (b) serum levels variations observed in the three studied groups at times T0 e T1. Abbreviations: PGI: pepsinogen I; G17: gastrin 17.

Table 6. Absolute values and relative percentages of patients subdivided, in each group, based on the type of response to the therapy (ineffectiveness, effectiveness, high effectiveness). The indicators considered were PGI increase, G17 reduction and symptoms variation. Abbreviations: PGI: pepsinogen I; G17: gastrin 17

Indicators	Ineffectiveness N. patients/total (%)	Effectiveness N. patients/total (%)	High effectiveness N. patients/total (%)
Group 1: L-cysteine			
PGI increase	44/70 (62.9)	11/70 (15.7)	15/70 (21.4)
G17 reduction	41/70 (58.6)	19/70 (27.1)	10/70 (14.3)
Symptoms variation	24/70 (34.3)	16/70 (22.8)	30/70 (42.9)
Group 2: zinc L-carnosine			
PGI increase	59/75 (78.6)	8/75 (10.7)	8/75 (10.7)
G17 reduction	31/75 (41.3)	27/75 (36.0)	17/75 (22.7)
Symptoms variation	17/75 (22.7)	21/75 (28.0)	37/75 (49.3)
Group 3: No therapy			
PGI increase	39/50 (78.0)	7/50 (14.0)	4/50 (8.0)
G17 reduction	39/50 (78.0)	10/50 (20.0)	1/50 (2.0)
Symptoms variation	30/50 (60.0)	6/50 (12.0)	14/50 (28.0)

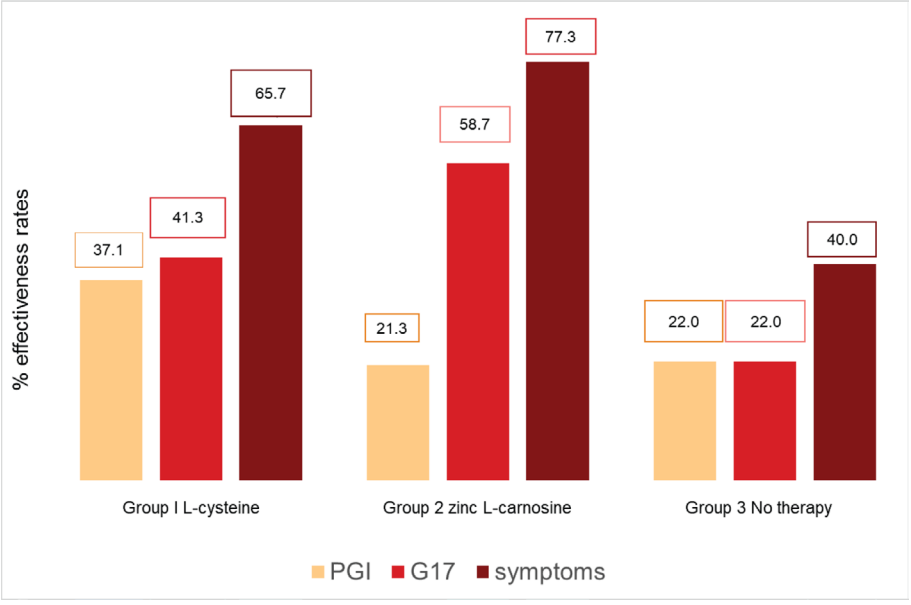

Figure 4. Effectiveness percentage rates of pepsinogen I, gastrin 17 serum levels and symptoms after L-cysteine (Group 1) and zinc L-carnosine (Group 2) therapy or no therapy (Group 3). Abbreviations: PGI: pepsinogen I; G17: gastrin 17.

Tolerability of L-cysteine and zinc L-carnosine

The results on tolerability generally agreed with what was described in the technical data sheet of the two medical devices. Most patients experienced no tolerability problems. Two patients belonging to Group 1 described nausea and epigastric pain; despite this, they continued with the therapy until the end of the study.

For this reason, they were not classified as drop-out cases. Otherwise, two patients belonging to Group 2 were forced to interrupt therapy: the first due to the onset of glossitis and haemorrhoidal pathology, the second due to a hacking cough. Suspension of intake resulted in the resolution of the adverse events.

Discussion

The patient who suffers from CAG presents, in 50%-60% of cases, dyspeptic symptoms associated with early satiety and/or postprandial fullness. A subset of the population with body-fundus atrophy does not report any disorder, but some alarm signs, such as an anemic state. After diagnosis of CAG. the only possible approach is monitoring the atrophic evolution and adopting strategies able to prevent or slow down its progression and alleviate symptoms. To date, even if scientific research is continuously looking for therapeutic solutions, there is no pharmacological treatment for CAG resolution or its regression. Given the phlogistic nature of the atrophic process, recently the attention of the scientific world focused on the use of molecules with anti-inflammatory, detoxifying, antioxidant and reparative action on the gastric mucosa. Among them, L-cysteine, (L-cysteine) and zinc L-carnosine, (zinc L-carnosine) would appear to be of some clinical utility.

Population

Before the assignment of therapeutic protocols, patients who came to the check-up were indagated on their demographic characteristics, presence and type of symptoms and blood-chemical profile. Age, gender, BMI and smoking and alcohol habits did not show statistically significant differences between the three cohorts indicating that the conditions of recruitment were quite similar. As regards symptoms, our results confirm what is reported in the literature (7,50), in particular about pain (21.9%) and gastroesophageal reflux (8.5%) in the global population. The presence and the type of symptoms detected at baseline were not different between the three groups. Considering the whole CAG population enrolled for the study, 27.0% of patients did not report any symptoms at time T0.

Overall, the lack of significant differences for the variables relating to symptoms, anemic status and hematological-chemical parameters is expressive of the cohort's homogeneity at time T0.

Only folic acid serum levels were different in the three groups, probably due to the concomitant supplementation of this molecule by some patients at the time of enrollment. Higher serum values of chromogranin were found in Group 3 compared to Groups 1 and 2 at time T0. Chromogranin is a marker of progression to the neuroendocrine tumor; considering that patients in Group 3 had not been assigned for any therapy, as they formed the control group, this data could suggest a bias in the selection of patients for treatment. It should be remembered, however, that the recruitment was carried out in a randomized way and did not take into account the patient's baseline parameters for selection. Furthermore, higher chromogranin values were probably due to the interference exerted by the residual effect of other drugs (protonic pump inhibitors) before enrollment in the study period.

In the total population, as well as in the three study groups individually considered, the majority of CAG was diagnosed at moderate-severe histological grade (OLGA II and III); however, no significant differences were detected in the distribution of OLGA stage results. Regarding the etiological aspect, the distribution of patients affected by A-CAG or mixed CAG was substantially similar albeit with a shift towards the autoimmune type of gastritis. This agrees with what has already been described in the literature (5) indicating the similar nature of pathogenic, autoimmune and infectious, noxa.

Gastric function evaluation

The typical CAG serological phenotype is represented by reduced secretion of PGI, consequent to hypo/achlorhydria, and increased stimulation of G17 released in response to low gastric acidity via a negative feedback mechanism (6). Usually, any variation in both parameters allows for monitoring the worsening of atrophic status together with a periodic endoscopic evaluation. The short time for the study did not allow us to take into consideration a new endoscopic exam to establish the therapeutic efficacy; however, given

sensitivity and specificity characteristics for PGI and G17 in identifying a pre-cancerous condition, these two parameters were chosen as therapeutic effectiveness monitoring indicators together with symptoms.

Analyzing the three groups individually, a significant decrease in PGI and PGII was detected in Group 1 with respect to Groups 2 and 3; a greater increase in G17 was found in Group 2 compared to the other groups without, however, reaching the statistical significance. Regarding anti-Hp IgG antibodies, the differences between groups could be explained by the greater frequency of patients with autoimmune and Hp comorbidity. These differences, observed at time T0, were probably due to the casual recruitment of patients and did not take into account the clinical functional status of atrophy in each patient.

Comparisons of histological and serological diagnosis demonstrated that, as the stage of atrophy increased, there was a gradual reduction in circulating PGI levels and a progressive increase in G17. However, starting from stage III and more markedly in stage IV, G17 values showed a decline. This finding may pathophysiologically be explained considering that, in the advanced phase of atrophy, not only parietal and chief cells, but also G cells, responsible for the synthesis and secretion of G17, are missing. This is particularly true when the antral area of the stomach, where cells with an endocrine function are located, is compromised.

Therapeutic efficacy of L-cysteine and zinc L-carnosine

L-cysteine is a natural semi-essential amino acid involved in the reaction with acetaldehyde which accumulates at the gastric level following the introduction of alcohol and smoking, but also after food intake in the presence of achlorhydria; it is able to covalently bind acetaldehyde producing a stable and inert compound that is eliminated mainly through feces (81). In our therapeutic protocol, L-cysteine was found to be effective for increasing PGI and lowering G17 values; the best efficacy rate was, however, highlighted on the symptoms with an improvement or no appearance of new symptoms during the observation period (65.7% rate).

The results we obtained for L-cysteine confirm what was found in a recent study on a cohort of 77 patients affected by CAG subjected to treatment with L-cysteine (100 mg x 3/day) for one year; after three, six and twelve months the authors observed a progressive increase in PGI from 7.88 to 15.92 ng/mL and a gradual reduction in G17 from 30.31 to 19.23 pmol/L (82). These results were confirmed in a subsequent two-year follow-up study in which a statistically significant improvement in symptoms was detected ($p < 0.01$) only in patients treated with L-cysteine, but not in those untreated (83). Recovery of gastric secretion in terms of increased PGI levels could be important in limiting the production of acetaldehyde in the stomach. The decline in G17 levels is another important evidence taking into account the role of this hormone as a cell growth factor in the pre-neoplastic condition (82).

Zinc L-carnosine is formed by the combination of zinc and L-carnosine, two substances naturally present in the human body. In the stomach, particularly in the ulcerated site, it gradually releases zinc, prolonging the local therapeutic effects both in terms of cellular adhesion and diffusion of zinc in the tissues; at the site of injury, it is captured by transporter proteins, allowing L-carnosine to be locally released. The combination of these events can contribute to the healing of gastric lesions and ulcers by stimulating cell repair and promoting mucosal regeneration (70-71,84-85). As regards the therapeutic efficacy of zinc L-carnosine in the treatment of CAG, there is no robust scientific evidence. Preliminary evaluations would indicate promising results, especially in terms of improvement of symptoms (reduction of dyspepsia and heartburn), in particular in infectious CAG (86). Our data demonstrated a lower efficacy on PGI, but greater on G17 after treatment with zinc L-carnosine, as compared to L-cysteine; the improvement in symptoms or the absence of new symptoms was better in patients treated with zinc L-carnosine concerning untreated ones (rate of 77.3% vs. 65.7%).

Our preliminary observations suggest that the clinical efficacy of L-cysteine and zinc L-carnosine are similar although there are differences probably related to different mechanisms of action. L-cysteine seems to act more specifically on increasing serum PGI levels through inactivation of acetaldehyde produced by the metabolic activity of bacteria ingested with food or alcoholic beverages; zinc L-carnosine would have a

greater influence on lowering G17 values thanks to the combined effects on gastric mucosa protection, greater mucus production and anti-inflammatory and antioxidant action.

CAG, in the cascade of events leading to the development of carcinoma, represents a critical event; it's the last stage in which a partial recovery of the atrophic picture may be possible. To demonstrate this assumption, it would have been useful to compare the histological data before and after treatment; however, the follow-up period was too short either to submit patients to a new endoscopic examination or to detect potential changes in gastric morphology. The use of PGI and G17 for the medium-term study was pertinent, considering that the changes in functional parameters are more immediate than the morphological ones. Although useful, this evaluation was not sufficient to establish the therapeutic efficacy of both molecules; therefore, we also considered variations in symptoms from time T0 to T1. Surprisingly, the cumulative findings showed an improvement in the clinical picture. This result is completely new since, to our knowledge, there is no published work on the matter, nor any data on the comparison between both devices is available.

Tolerability of L-cysteine and zinc L-carnosine

The short time of the study did not allow for a critical evaluation of the occurrence of adverse events following the administration of L-cysteine and zinc L-carnosine.

Despite being commonly present in foods, to date, there is not enough information to know whether L-cysteine is safe when introduced in high doses or what side effects could have. The systemic side effects of zinc L-carnosine, at usual therapeutic doses, are negligible. Only the most sensitive patients report any negative side effects limited to mild stomach cramps, nausea, vomiting, constipation and diarrhea; they tend to disappear when treatment is suspended (85). Most patients in our study experienced no tolerability issues with L-cysteine; only two reported nausea and epigastric pain, but they continued with the therapy until the conclusion of the study. In this case, a causal link with the drug assumption could be hypothesized.

As regards zinc L-carnosine, literature evidence reports a potential problem with the administration of zinc at high doses and for prolonged periods the possible induction of copper deficiency. However, no important adverse events have been described at the doses used by us. In our series, two patients belonging to Group 2 were forced to immediately interrupt the administration of zinc L-carnosine, the first due to the onset of glossitis and haemorrhoidal pathology, and the second due to a hacking cough. The suspension of treatment led to the resolution of the adverse events, therefore it is possible to hypothesize a correlation between the unfavourable episode and the use of this medical device.

Limits of the study

The present study shows some limitations. Firstly, the short duration (three months) of therapeutic follow-up. Furthermore, the results observed on a relatively limited number of patients may not reflect what happens in a larger population of subjects affected by CAG; however, our numerical series was comparable to that of other studies that take into consideration the effect of these molecules on other pathologies of the gastrointestinal tract (85).

Another limitation concerns the choice to study patients with CAG of different etiology as a single entity without differentiating the autoimmune type from the mixed one. Probably, treatment with L-cysteine in the group of patients with Hp-related atrophy (characterized by strong production of acetaldehyde) could show greater beneficial effects compared to the cumulative population; alternatively, zinc L-carnosine could have a different effect in the cohort with autoimmune atrophy alone compared to that with Hp atrophy due to reduction of the inflammatory picture.

Conclusions

In this preliminary work, the effect of L-cysteine and zinc L-carnosine in the treatment of CAG is compared for the first time. Therapeutic effects, considered in terms of improvement in gastric function and

symptoms, have been documented with both medical devices, even if in different ways. Both appear well tolerated by patients; side effects are limited to mild manifestations that resolve after stopping therapy.

However, further prospective randomized multicenter studies performed in double-blind on larger series and individual pathology groups are necessary to further confirm and strengthen these preliminary data.

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Authors Contribution: MPP, SR: research concept and study design, draft of the manuscript; KIR-C, AF, LB, AV: data collection and assembly; MF: data collection, data analysis and interpretation; PC, FDM, LF: critical revision of the article. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work ere appropriately investigated and resolved. They approved the final version.

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Correspondence:
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Pellegrino Crafa,
Department of Medicine and Surgery, University of Parma, Italy
Via Gramsci 14, 43126 Parma
E-mail: pellegrino.crafa@unipr.it
ORCID: 0000-0001-8603-863X

Appendix – Supplementary files

Table S1. The questionnaire modified UGISQUE.

Symptoms Questionnaire (Modified UGISQUE)								
	Severity of the symptoms							
SYMPTOMS*	Absent (0)		Mild (1-3)		Moderate (4-6)		Severe (7-10)	
	T	T1	T	T	T0	T1	T0	T1
Pain								
• **Epigastric pain**								
• **Abdominal pain**								
Reflux								
• **Acid reurgitation**								
• **Belching**								
• **Heartburn**								
• **Globus pharyngeus**								
• **Hippcup**								
• **Sialorrhea**								
Maldigestion								
• **Aerophagia**								
• **Bitter taste in the mouth**								
• **Bloating**								
• **Flatulence**								
• **Nausea**								
• **Rumbling in the stomach**								
Non-specific symptoms								
• **Anemia**								
• **Asthenia**								
• **Dysphagia**								
• **Weight loss**								
• **Vomiting**								
Extra-digestive symptoms								
• **Chest pain**								
• **Cough**								
• **Dyspnea**								
• **Glossitis**								
• **Laryngitis/Pharyngitis**								
• **Tachycardia**								

*Symptomatic patients were defined as those who reported discomfort in at least one item. Abbreviations: T0: symptoms at baseline; T1: symptoms after 3 months of therapy.