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Oral citicoline: Influence of long-term therapy on perimetric glaucoma defects

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3. Figures 12
   Version: 1
   Description: Figure 1 – Mean Deviation (MD) trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.
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4. Figures 13
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5. Figures 14
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   Description: Figure 3 – Glaucoma Staging System 2 (GSS2) stage trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.
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6. Figures 15
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7. Figures 16
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8. Supplementary Digital Material 1
   Version: 1
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Dear Editor-in-Chief Prof. Benzo:

The manuscript "Oral citicoline: Influence of long-term therapy on perimetric glaucoma defects" is being resubmitted as “letter to the Editor”, as requested by the journal.

Thank you for your consideration.

We look forward to hearing from you.

Best Regards

Prof. Elena Pacella

Title: Oral Citicoline: Influence of long-term therapy on perimetric glaucoma defects

Running title: long-term therapy with Citicoline and perimetric defects

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To the Editor:

Primary Open Angle Glaucoma (POAG) is characterized by a gradual loss of retinal ganglion cells (RGCs). Visual impairment ranges from visual field defects to blindness. Intraocular pressure (IOP) is the primary risk factor for POAG progression [1,2]. However, recent studies suggest that therapy cannot be limited to IOP lowering alone. In fact, despite adequate IOP control, the disease still progresses in a percentage of patients [3]. In these, vascular or mechanical neurodegenerative processes are likely responsible. Therefore, the current trend is to prescribe molecules capable of inhibiting RGCs apoptosis. Citicoline, also known as choline CDP, is an endogenous organic neuroprotective molecule and acts as an intermediary in phosphatidylcholine synthesis. Growing evidence suggests that it stimulates neural cell metabolism, inhibits phospholipids degradation, and possibly even apoptosis. [4]. For this purpose, authors performed a retrospective study to explore the effect of citicoline supplementation on visual field defects progression.

The study recruited 60 subjects with POAG (33 males, 27 females; average age: 69.2 years; minimum age: 44 years; maximum age: 86 years). These were all 4th stage POAG on the GGS2 classification system. A third group of 30 healthy subjects was included as control (Healthy Group - HG). HG subjects did not suffer from ocular diseases or systemic comorbidities (hypertension or diabetes mellitus, among others), and their visual fields were normal. All three groups were comparable for age and gender. Inclusion criteria: POAG (IV grade on the Shaffer classification); IOP effectively controlled with hypotensive therapy (<18 mmHg); corneal pachymetry within the following range: > 520µm and < 550µm. Exclusion criteria: ocular pathologies other than POAG; opacities of the dioptric mediums. POAG subjects were divided in two groups: Therapy Group (TG) received oral citicoline plus conventional hypotensive therapy. Oral 500 mg citicoline was prescribed daily for two consecutive months, then suspended for one month. The Control Group (CG) received hypotensive therapy alone. Perimetry using the Humphrey Perimeter (Humphrey program 30-2 HFA II and SITA

Standard threshold strategy) was obtained from each participant at baseline as well as 12, 24, and 36 months post enrollment. Outcome measures included: Mean Deviation (MD) and Pattern Standard Deviation (PSD) values on perimetry testing, best corrected visual acuity (BVCA), POAG stage (Glaucoma Staging System 2), and IOP. Groups were compared using the Student's t test for paired samples. The computations were made using the SPSS software v. 22.0 for Microsoft Windows. Statistical significance was set at $P < 0.05$. This study was approved by the Institutional Review Board of La Sapienza University of Rome (Protocol No. 1076/14). All participants signed a written consent form upon enrollment. This study was performed in accordance with the tenets of the Declaration of Helsinki.

As shown in Figures 1 and 2 and Tables I - IV, TG subjects showed a statistically significant improvement in both the mean MD and mean PSD scores, when comparing T0 with T36 ($P = 0.001$). No statistically significant changes in the mean MD and PSD scores were noted in the other two groups ($P > 0.05$). Figure 3, Tables V and VI indicate a shift of the mean GSS 2 Stage towards better values among TG subjects, when comparing T0 and T36 ($P = 0.001$). No statistically significant changes in the mean GSS 2 Stage were noted among CG or HG ($P > 0.05$). Figure 4 shows that TG subjects showed an improvement in BCVA ($P < 0.05$). CG subjects did not. Figure 5 shows mean IOP values. All the recorded IOP values were below 18 mmHg. This indicates adequate IOP control. IOP fluctuations were not statistically significant.

The increase of MD score towards less negative values and the reduction of the PSD score indicate an improvement in retinal sensitivity at follow-up visual field testing [5]. Conversely, a decrease of the MD score towards more negative values and the increase of the PSD score indicate the opposite, that is a decrease in retinal sensitivity secondary to RGC loss (Figures 1 and 2). As previously mentioned, POAG progresses in a subset of patients despite adequate IOP control. Recent studies have explored the role of citicoline in halting disease progression in this subset of patients. Citicoline

has been shown to improve retinal sensitivity, PERG and PEV parameters, and reduce scotoma expansion [4].

In the present study, oral administration of citicoline led to a significant improvement in the perimetry indices in TG subjects. Changes equated to a 35% increase (less negative) in the mean MD score and a 16% decrease in the mean PSD score, when comparing T0 with T36. This indicates a statistically significant improvement (p-value = 0.001) of the retinal sensitivities (Figure 4). On the contrary, CG subjects showed a decrease towards more negative values of the mean MD score and an increase of the mean PSD score, but this change was not statistically significant ($P > 0.05$). Progression of the MD score towards more negative values and progression of the PSD score towards more positive values is indicative of visual field defects progression. These results suggest the potential role of using citicoline in addition to hypotensive therapy to halt POAG disease progression.

In summary, the therapeutic association with oral 500 mg citicoline assumed daily has shown a promising neuroprotective effect on RGCs.

Abbreviations found in this article:

POAG: Primary Open-Angle Glaucoma

RGCs: Retinal Ganglion Cells

IOP: Intraocular Pressure

MD: Mean Deviation

PSD: Pattern Standard Deviation

GSS2: Glaucoma Staging System 2

TG: Therapy Group

CG: Control Group

HG: Healthy Group

Table I: Comparison of Median Deviation (MD) scores between groups: Control, Health, and Therapy. The table shows the mean ± standard deviation (SD).

MD score	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control Group	-14±6.1	-14±3.9	-15±4	-15±4
Healthy Group	0.1±1	0.2±1.1	0.2±0.7	0.1±0.6
Therapy Group	-14±3.2	-11±2.4	-9±4	-8.8±3.8

Table II: Relative change in the Median Deviation score for each group, as compared to previous value. Student's t test for paired samples. (*). P value > 0.05 is statistically significant.

MD score	T0- T12 (Δ)	p-value	T0- T24 (Δ)	p-value	T0- T36 (Δ)	p-value
Control Group	-7%	0.151	-6%	0.211	-7%	0.151
Healthy Group	<1%	0.333	<1%	0.353	<1%	0.233
Therapy Group	+21%	**0.001(*)**	+35%	**0.001(*)**	+35%	**0.001(*)**

Table III: Comparison of Pattern Standard Deviation (PSD) scores between groups: Control, Health, and Therapy. The table shows the mean ± standard deviation (SD).

PSD score	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control Group	13±3.9	13±4	13±2.8	13±3
Healthy Group	2±0.6	2±0.1	2±0.7	2±0.3
Therapy Group	13±3.2	13±2.6	12±4.2	11±3

Table IV: Relative change in Pattern Standard Deviation (PSD) score in each group, as compared to previous values. Student's t test for paired samples. (*). A p value > 0.05 is statistically significant.

PSD	T0- T12 (Δ)	p-value	T0- T24 (Δ)	p-value	T0- T36 (Δ)	p-value
Control Group	<1%	0.654	<1%	0.222	<1%	0.151
Healthy Group	<1%	0.432	<1%	0.272	<1%	0.295
Therapy Group	<1%	0.234	-7%	0.752	-16%	**0.001(*)**

Table V: GSS2 Stage comparison between groups: Control, Health, and Therapy. The table shows the mean ± standard deviation (SD).

GSS2 Stage	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control Group	4±1.5	4±1.6	4±1.1	4.2±1.6
Healthy Group	0	0	0	0
Therapy Group	4.1±1.4	3.4±1.3	2.7±1.2	3±1.3

Table VI: Relative percentage differences (Δ) between the times divided by groups. Student's t test for paired samples. (*). A p value > 0.05 is statistically significant.

GSS2 Stage	T0- T12 (Δ)	p-value	T0- T24 (Δ)	p-value	T0- T36 (Δ)	p-value
Control Group	<1%	0.255	<1%	0.512	+2%	0.413
Healthy Group	<1%	0.125	<1%	0.212	<1%	0.313
Therapy Group	-12.8%	0.068	-30%	**0.001(*)**	-35%	**0.001(*)**

Figure legends

Figure 1 – Mean Deviation (MD) trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.

Figure 2 – Pattern standard deviation (PSD) trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.

Figure 3 – Glaucoma Staging System 2 (GSS2) stage trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.

Figure 4 – Best-corrected visual acuity (BVCA) as a function of time (Times 0, and 12, 24, and 36 months) and therapy.

Figure 5 – Mean intraocular pressure (IOP) trend as a function of time (Times 0, and 12, 24, and 36 months) and therapy.

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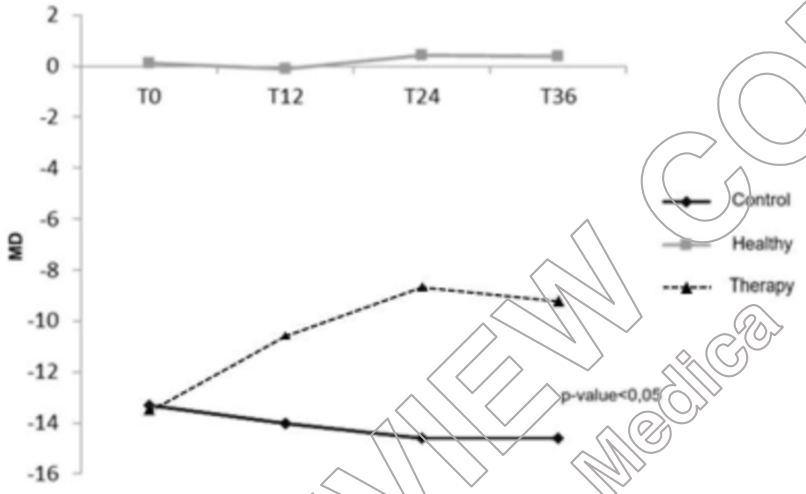
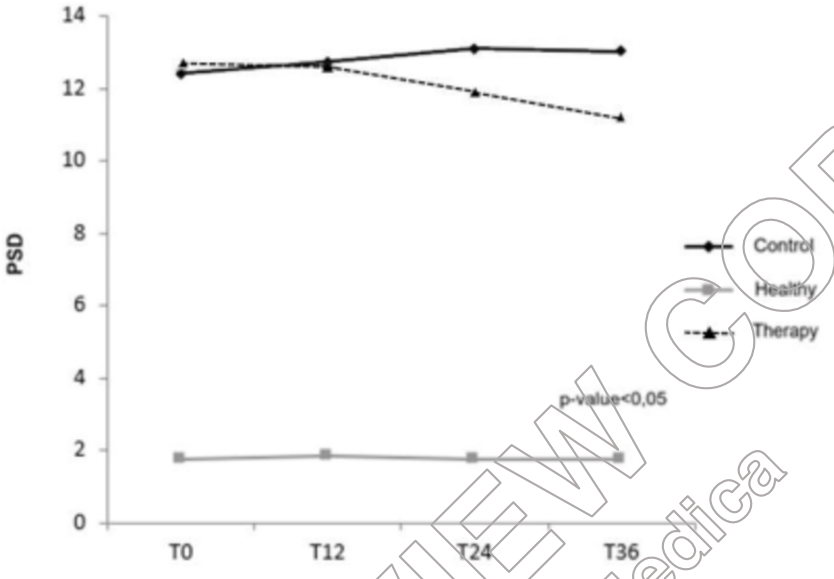


Figure 1.



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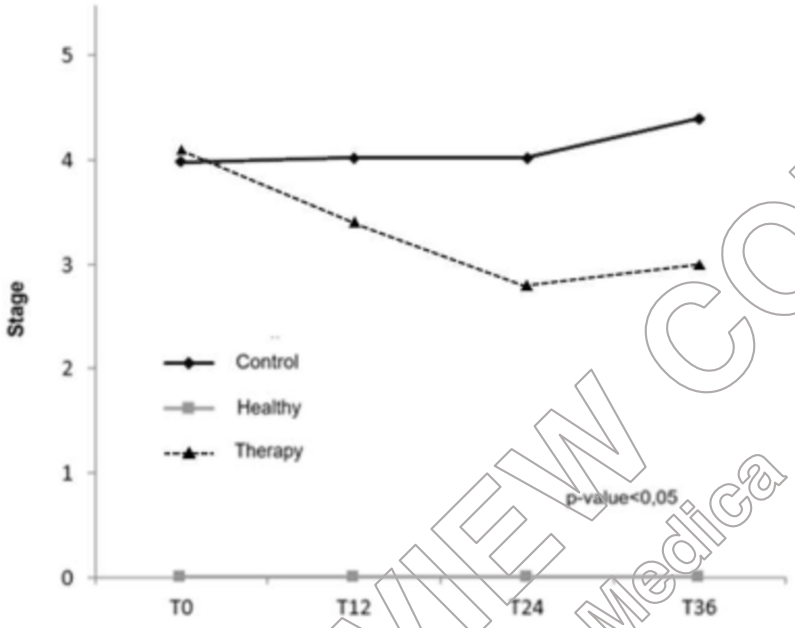

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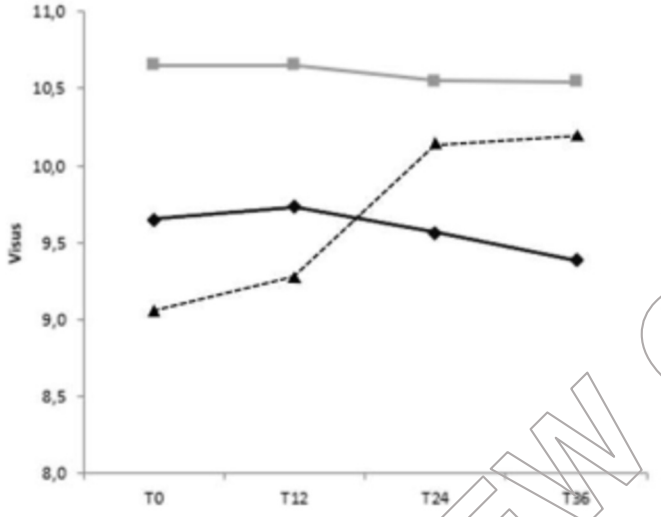

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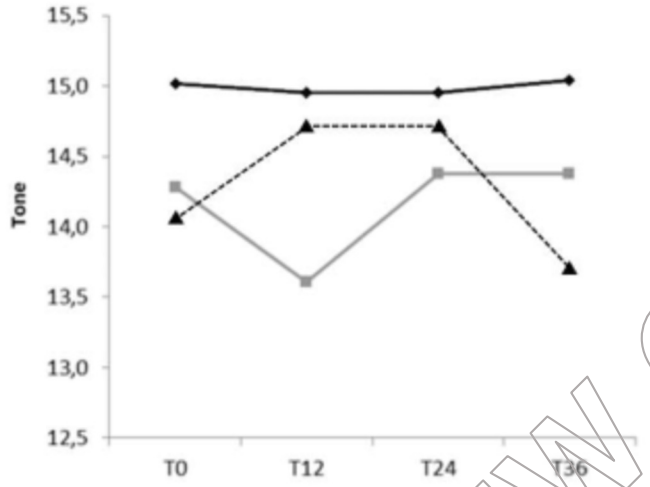

Figure 5

Supplementary Digital Material

Download supplementary material file: Panminerva Med-4005_Supplementary Digital Material1_V1_2020-08-09.docx