Pharmacological Research 191 (2023) 106702

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Beneficial effects of L-Arginine in patients hospitalized for COVID-19: New insights from a randomized clinical trial

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ARTICLE INFO

Keywords:
Arginine
COVID-19
Critical Care
Cytokine storm
Inflammation
IL-6
IL-2
IFN-γ
IL-10
Lymphocytes

ABSTRACT

We have recently demonstrated in a double-blind randomized trial the beneficial effects of L-Arginine in patients hospitalized for COVID-19. We hypothesize that one of the mechanisms underlying the favorable effects of L-Arginine is its action on inflammatory cytokines. To verify our hypothesis, we measured longitudinal plasma levels of pro-inflammatory and anti-inflammatory cytokines implied in the pathophysiology of COVID-19 in patients randomized to receive oral L-Arginine or placebo. The study was successfully completed by 169 patients. Patients in the L-Arginine arm had a reduced respiratory support evaluated at 10 and 20 days; moreover, the time to hospital discharge was significantly shorter in the L-Arginine group. The assessment of circulating cytokines revealed that L-Arginine significantly reduced the circulating levels of pro-inflammatory IL-2, IL-6, and IFN-γ and increased the levels of the anti-inflammatory IL-10. Taken together, these findings indicate that adding L-Arginine to standard therapy in COVID-19 patients markedly reduces the need of respiratory support and the duration of in-hospital stay; moreover, L-Arginine significantly regulates circulating levels of pro-inflammatory and anti-inflammatory cytokines.

1. Introduction

We and others have demonstrated that endothelial dysfunction contributes to coronavirus disease (COVID-19)-associated acute respiratory distress syndrome [1–15].

The amino acid L-Arginine has been previously shown to improve endothelial function [16–20]. Specifically, in a double-blind randomized, placebo-controlled trial, we have recently established the beneficial effects of adding oral L-Arginine to hospital standard-therapy in patients hospitalized for COVID-19 **(**NCT04637906**)** [21]; however, the exact mechanisms have not been explored.

Based on reports showing anti-inflammatory effects of L-Arginine *in vitro* [22,23] and in preclinical models [24], we hypothesized that one of the mechanisms underlying the favorable effects of L-Arginine, alongside the known improvement of endothelial dysfunction [25], could be its action on the circulating levels of inflammatory cytokines.

2. Methods

2.1. Study design and procedures

Details on the study design, inclusion and exclusion criteria, procedures, outcomes to be assessed, and statistical analyses have been reported in the published protocol [21].

2.2. Ethical approval

The Study was approved by the institutional Ethical Committee (A.O. R.N. "Ospedali dei Colli", Naples, Italy); written informed consent was collected from all patients, or their legal representative if they were

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https://doi.org/10.1016/j.phrs.2023.106702
Received 24 January 2023; Received in revised form 3 February 2023; Accepted 14 February 2023
Available online 15 February 2023
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unable to provide consent. The trial was performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice guidelines.

2.3. Cytokine measurements

We assessed longitudinal plasma levels of IFN-γ, IL-2, IL-6, and IL-10, which have been implied in the pathophysiology of COVID-19 [26–30]. Circulating levels of cytokines were measured on hospital admission and after 2 weeks, through ELISA, as previously described [29]. Details on the study design, inclusion and exclusion criteria, procedures, outcomes to be assessed, and statistical analyses have been reported in the published trial [21].

2.4. Statistical analyses

Data were analyzed by *SPSS* (version 26.0; SPSS, IBM, Armonk, USA) and by the open software *jamovi* (version 2.3.16.0) and expressed as mean±SD or numbers and percentage, as appropriate. Differences in cytokine expression were assessed *via* ANOVA followed by Tukey *post hoc* correction. The null hypothesis was rejected at a two-tailed $p < 0.05$.

3. Results

A total of 169 patients successfully completed the study (please see the flowchart shown in Fig. 1): 84 randomized to receive placebo, 85 to L-Arginine. A 100 % protocol adherence was achieved. All patients were randomized and received the assigned treatments with a mean of 7.8 days after symptoms onset. The main characteristics of the patients are shown in Table 1.

At 10-day evaluation, 31 % in the placebo group and 82 % in the L-Arginine group had reduced the respiratory support (Fig. 2**A**). A multivariable logistic regression analysis was performed in order to examine the magnitude of association between the treatment with L-Arginine and the primary outcome: when adjusting for potential confounders including age, gender, C-reactive protein, P/F ratio, and use of monoclonal antibodies, the odds of having a reduction in respiratory support were 6.27-fold higher in those who were in the L-Arginine group compared to those in the placebo group (OR:6.27; 95 %CI: 2.08–18.87; $p = 0.001$). Furthermore, 20 days after randomization we detected a significant difference in the primary outcome between the two study arms (Placebo group: 5 out of 56, 9 %; L-Arginine group: 11 out of 15, 73 %; $p < 0.0001$; Fig. 1). On the contrary, changes in P/F ratio at 10 and 20 days were not significantly different (Table 1).

Among the secondary outcome measures, differences between active treatment group *vs* placebo group were significantly different only for the time to hospital discharge, which was significantly shorter in the L-Arginine arm (22 ± 8 *vs* 36 ± 15 days, $p < 0.0001$; Fig. 2**B**) and was confirmed in a Cox regression analysis using a fully adjusted multivariable model including age, gender, and C-reactive protein (HR:4.06; 95 %CI: 2.62–6.32; $p < 0.0001$). The rate of lymphocyte number normalization and the time to obtain a negative RT-qPCR for SARS-CoV-2 on nasopharyngeal swab were similar between the 2 groups.

Strikingly, the evaluation of circulating cytokines revealed that L-Arginine treatment significantly reduced the pro-inflammatory IL-2, IL-6, and IFN-γ while increasing the levels of the anti-inflammatory IL-10 (Fig. 3).

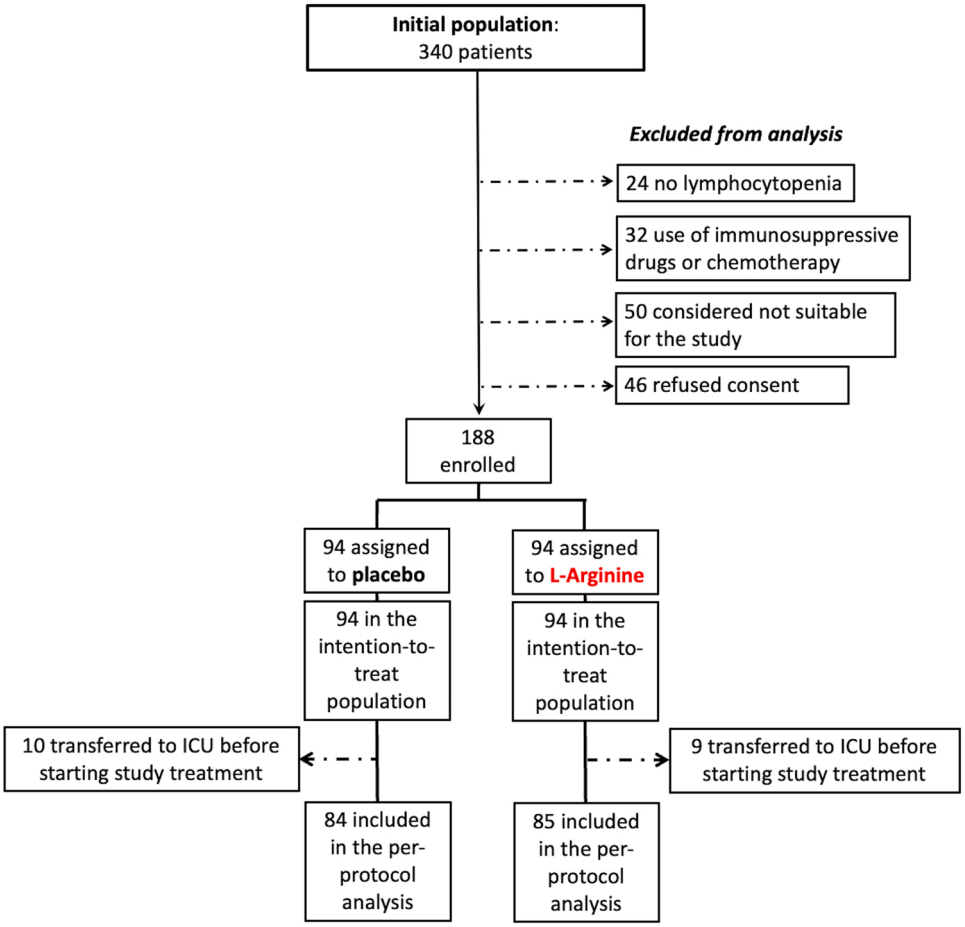

Fig. 1. Flowchart of the study.

Table 1
Main characteristics of the two study groups. Data are presented as means ± SD for continuous variables; percentages are reported for categorical variables. ALT: Alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CPAP: continuous positive airway pressure; CRP: C Reactive Protein; HFNC: high-flow nasal cannula; LMWH: low molecular weight heparin; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation.

	Placebo (n = 84)	L-Arginine (n = 85)	p
Gender (M/F, %)	75.3/34.7	64.7/35.3	0.137
Age (years)	62.0 ± 11.9	61.1 ± 13.2	0.634
Hypertension (%)	46.9	37.6	0.227
Coronary artery disease (%)	14.8	17.6	0.621
Smokers (%)	13.6	11.8	0.725
Obesity (%	9.9	10.6	0.880
Diabetes (%)	11.1	11.8	0.895
Time between onset of symptoms and admission (days)	7.9 ± 3.1	7.9 ± 3.3	0.982
White blood cells (n/mL)	8521.4 ± 5103.6	7709.4 ± 4222.2	0.265
Lymphocytes (n/mL)	796.8 ± 362.4	782.1 ± 329.4	0.788
CRP (mg/L)	8.0 ± 6.7	11.1 ± 10.4	0.029
D-dimer (ng/mL)	945.5 ± 1660.6	709.7 ± 1157.2	0.295
ALT (U/L	62.9 ± 82.7	53.2 ± 44.5	0.351
AST (U/L)	46.3 ± 40.1	40.8 ± 29.0	0.312
Creatinine (mg/dL)	0.89 ± 0.7	0.78 ± 0.2	0.100
Sodium (mmol/L)	138.5 ± 4.1	138.5 ± 4.6	0.946
Potassium (mmol/L)	4.44 ± 0.7	4.40 ± 0.5	0.690
Asthenia (%)	63.0	63.5	0.940
Dyspnea (%)	91.4	89.4	0.671
Cough (%)	37.0	32.9	0.580
Fever (%)	67.9	75.3	0.291
Sputum (%)	8.6	2.4	0.074
Remdesivir (%)	39.5	44.7	0.498
LMWH (%)	95.1	92.9	0.566
Steroids (%)	86.4	92.9	0.166
Monoclonal antibodies (%)	15.4	10.0	0.472
Anti-COVID vaccine (%)	45.7	47.1	0.859
P/F (PaO_2/FiO_2 - baseline)	132.0 ± 57.5	148.6 ± 66.1	0.086
P/F (PaO_2/FiO_2 - day 10)	190.5 ± 116.3	216.8 ± 96.0	0.281
P/F (PaO_2/FiO_2 - day 20)	255.5 ± 103.4	258.8 ± 89.0	0.857
Hospitalization (days)	35.9 ± 15.4	21.9 ± 7.7	0.0001
Death	13 (13.8%)	3 (3.4%)	0.013
Respiratory support (baseline)			
None (%)	1.2	0	0.500
LTOT (%)	3.7	9.4	
HFNC (%)	77.8	71.8	
CPAP (%)	11.1	11.8	
NIV (%)	6.2	7.1	
Respiratory support (day 10)			
None (%)	7.4	49.4	< 0.0001
LTOT (%)	14.8	28.2	
HFNC (%)	67.9	20.0	
CPAP (%)	1.2	1.2	
NIV (%)	8.6	1.2	
Respiratory support (day 20)			
None (%)	22.2	81.0	< 0.0001
LTOT (%)	9.9	9.5	
HFNC (%)	65.4	9.5	
CPAP (%)	2.5	0	
NIV (%)	0	0	

4. Discussion

In addition to confirming in a larger population compared to the initial analysis [21] the beneficial effects of L-Arginine in patients hospitalized for COVID-19, we identified in the modulation of cytokines involved in the COVID-induced inflammatory response an unprecedented mechanism underlying the favorable effects of L-Arginine in COVID-19. These results are consistent with recent metabolomics

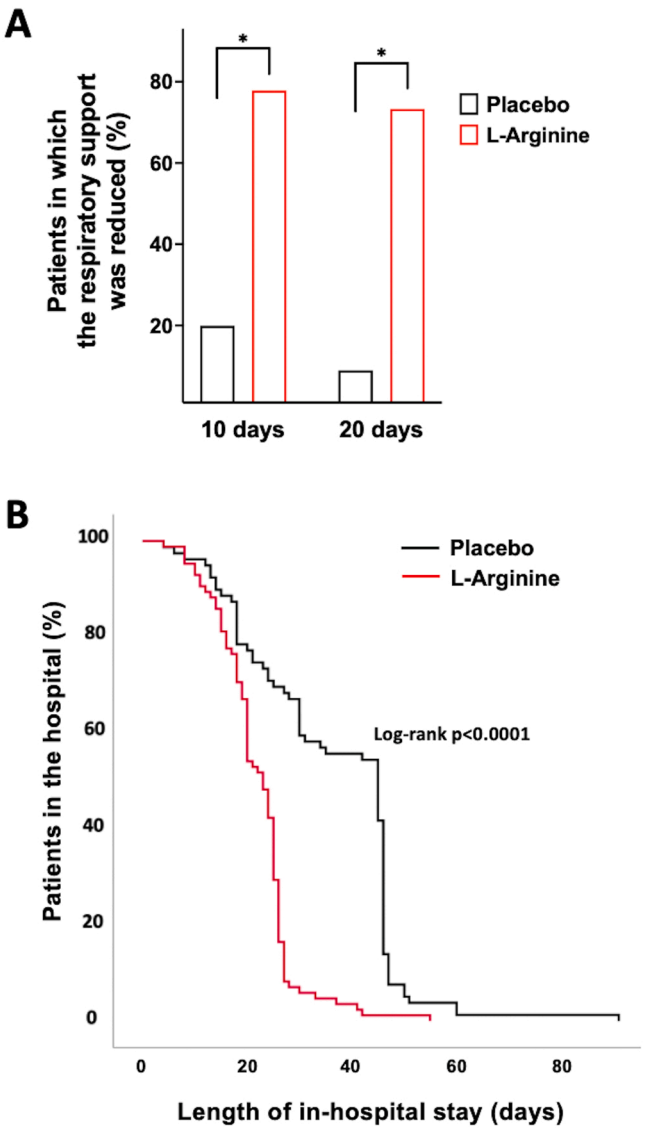

Fig. 2. Percentage of patients in which the respiratory support was reduced 10 days and 20 days after starting the therapy (**A**). Length of hospitalization examined in the L-Arginine and in the Placebo groups (**B**).

reports evidencing reduced circulating levels of L-Arginine in COVID-19 patients who experienced a severe outcome [31,32].

Of note, the peculiar modulation of both anti- and pro- inflammatory cytokines [33,34] is remarkable and emphasizes the key role of L-Arginine metabolism in COVID-19 [20,35,36]. Having observed that L-Arginine significantly reduces IL-6 levels is especially significant considering the recently published results of a secondary analysis of a Bayesian adaptive randomized clinical platform trial that included 4791 COVID-19 patients, showing that there was a greater than 99.9 % probability that sarilumab and tocilizumab (IL-6 receptor antagonists) improved survival through 6 months [37].

Our study is not exempt from limitations, including having measured only 4 cytokines, having enrolled exclusively patients hospitalized (which reduces the generalizability of our findings to patients with non-severe forms of COVID-19), and not having a population of patients with pulmonary disease not caused by COVID-19.

Further studies, ideally exploring more cytokines and chemokines, are warranted to dissect how exactly L-Arginine is able to modulate their circulating levels. Potential mechanisms by which L-Arginine exerts anti-inflammatory effects may include the reconstitution of circulating

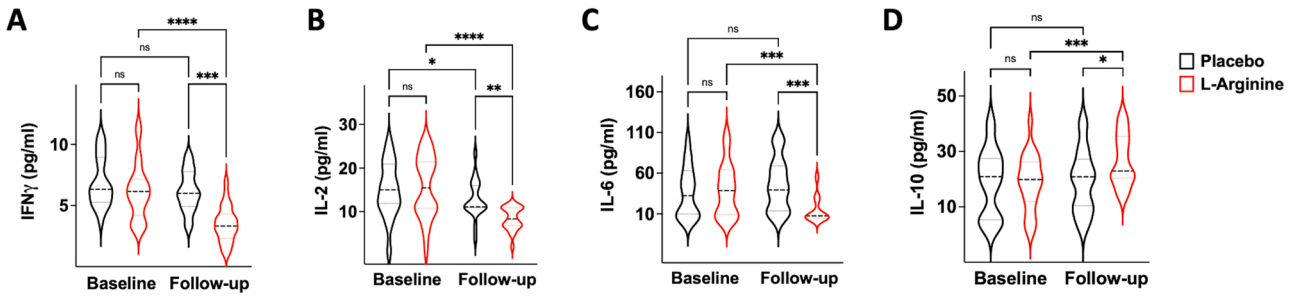

Fig. 3. Violin plots representing the circulating levels of IFN-γ, IL-2, IL-6, and IL-10 (**A–D**); *:p < 0.05; **:p < 0.01; ***:p < 0.005; ****:p < 0.001.; ns: non-significant (ANOVA and Tukey *post hoc* correction).

L-Arginine levels, a correction of nitric oxide dysfunction, and/or a direct action on immune cells [38–45].

Considering that favorable effects of L-Arginine, in combination with ascorbic acid, have been recently shown also in the so-called Long-COVID [36], dedicated investigations exploring the modulation of inflammatory markers in patients with Long-COVID are needed as well.

CRediT authorship contribution statement

Valentina Trimarco: Writing – original draft, Data curation, Formal analysis, Visualization. **Raffaele Izzo:** Writing – original draft, Data curation, Software. **Angela Lombardi:** Investigation, Visualization, Writing – review & editing. **Antonietta Coppola**: Investigation, Data curation, Visualization. **Giuseppe Fiorentino**: Data curation, Visualization. **Gaetano Santulli:** Conceptualization, Writing – review & editing.

Data Availability

Data will be made available upon reasonable request to the first Author(s).

Ethical Approval

The Study was approved by the institutional Ethical Committee of the Hospital (A.O.R.N. “Ospedali dei Colli”, Naples, Italy); written informed consent was collected from all patients, or their legal representative if they were unable to provide consent. The trial was performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice guidelines.

Sources of Funding

The Santulli’s Lab is supported in part by the National Institutes of Health (NIH): National Heart, Lung, and Blood Institute (NHLBI: R01-HL159062, R01-HL164772, R01-HL146691, T32-HL144456), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK: R01-DK123259, R01-DK033823), National Center for Advancing Translational Sciences (NCATS: UL1TR002556-06) to G.S., by the Diabetes Action Research and Education Foundation (to G.S.), and by the Monique Weill-Caulier and Irma T. Hirschl Trusts (to G.S.). This study was also supported by Grant 00014PRIN-2017 ID43237 to V.T.

Declaration of Competing Interest

None.

Acknowledgement

We thank Drs. Wang and Gambardella for helpful discussion.

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