Research Article

Early Treatment with a Peptide Derived from the Human Heat-Shock 60 Protein Avoids Progression to Severe Stages of COVID-19

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Abstract

Hyperinflammatory response induced by SARS-CoV-2 characterizes COVID-19 patients progressing to severe conditions. CIGB-258 is an immunoregulatory peptide with anti-inflammatory properties derived from the human stress protein 60 (HSP60). This peptide has been used in the treatment of serious and critically ill COVID-19 patients with positive results. This study is aimed to describe the outcomes of a cohort of moderately ill COVID-19 patients treated with CIGB-258. Clinical assessment and inflammation biomarkers indicated that these patients were progressing to the hyperinflammation phase. In addition, this study displays the outcomes of two other cohorts of COVID-19 patients in serious and critical conditions, treated with this molecule. One hundred and four patients with COVID-19 in moderate (18.3%), serious (60.6%) and critical (21.1%) conditions were enrolled in this study. None of the moderate patients progressed to the severe stage of the disease. Out of sixty-three seriously ill patients, only eleven progressed to a critical condition. These patients had several comorbidities that aggravated their clinical conditions.

Despite this, six of the patients who progressed to the critical condition recovered and were discharged from the hospitals. Out of twenty-two critically ill patients, only two died. Inflammatory biomarkers decreased after seven days of treatment. Also, IL-6 significantly decreased at 96 hours of the treatment. These results indicate that the early administration of CIGB-258 can improve the condition of moderately ill patients and avoid their progression to severe stages of COVID-19. This study confirms the capacity of this peptide to reduce the hyperinflammation characterizing this disease.

Keywords: COVID-19; CIGB-258; HSP60; Hyperinflammation; Jusvinza

1. Introduction

In December 2019, a novel pneumonia was reported in Wuhan, Hubei province in China. On February 11th, 2020, the World Health Organization (WHO) officially named it Coronavirus Disease 2019 (COVID-19), which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. The first case of COVID-19 in Cuba was reported on March 11th, 2020, just three months after first cases were reported in China [2]. Hyperinflammatory response induced by SARS-CoV-2 is the main cause of disease severity and death in infected patients [3, 4]. Several studies suggest that the pathophysiological basis of this severe inflammatory response is similar to the cytokine release syndrome [5-8].

During the progression to severe stages, patients significantly increased inflammatory biomarkers, Including Lactate Dehydrogenase (LDH), C-reactive Protein (CRP) and serum interleukin-6 [9-11]. Another severity biomarker is the Neutrophil/Lymphocyte Ratio (NLR). These predictors can identify patients who may progress towards severe phases of the disease [3, 12]. Drugs that inhibit inflammation at early stages are

crucial to avoid progression to the severe phase of COVID-19 [13, 14]. CIGB-258 is an altered peptide ligand derived from human cellular stress protein 60 (HSP60). This peptide inhibited the inflammation in several experimental models of Rheumatoid Arthritis (RA). CIGB-258 reduced the levels of the Tumor Necrosis Factor (TNFα), Interleukin (IL)-17 (IL-17) and interferon-γ (IFNγ) in preclinical studies [15-17] and in a phase I clinical trial with RA patients. Likewise, this molecule induced a significant decrease in autoantibodies against citrullinated self-proteins in RA patients [18]. Furthermore, this peptide increased the frequency of regulatory T cells (Treg) and their suppressive capacity against antigen-responding effector CD4+T cells from RA patients [19].

This peptide has been used in the treatment of serious and critically ill COVID-19 patients with positive outcomes [20, 21]. The drug received the Authorization for Emergency Use by the Cuban Regulatory Authority for the treatment of COVID-19 patients [22]. After this authorization, CIGB-258 received the name of Jusvinza. The inclusion of CIGB-258 in the Cuban national protocol approved by the Ministry of Public Health for COVID-19 took place on April 27th, 2020 [23]. The use of this drug has helped decrease fatality rate in Cuba. In April 2020, the fatality rate in Cuba was 4.16 [2] and in March 2021 it was 0.46 [24]. The therapy with CIGB-258 induces the inhibition of the activity of monocytes, macrophages and neutrophils in severe COVID-19 patients. This inhibition decreased IL-6, TNFa and IL-10 levels, and improved the NLR.

The therapeutic effects of CIGB-258 may also be enhanced by the progressive expansion of Treg. These cells migrate to inflammation sites inhibiting autoimmune damage on the endothelium, which is induced during SARS-CoV-2 infection [21]. These above results indicate that the early administration of CIGB-258 may avoid the progression to severe stages of COVID-19. Consistent with this idea, a cohort of moderate COVID-19 patients was included in this study. Clinical assessment and inflammation markers indicated that this cohort of patients was progressing to the hyperinflammation phase. The treatment with CIGB-258 stops progression to severe stages of COVID-19 in these patients. Furthermore, this study confirms the capacity of this peptide to reduce hyperinflammation in seriously and critically ill COVID-19 patients.

2. Materials and Methods

2.1 Patients

One hundred and four patients confirmed as SARS-CoV-2 positive by real-time reverse transcription polymerase chain reaction were enrolled in this study. Patients were recruited for the study between April 27th and October 7th, 2020, from eight Hospitals in Cuba. The patients' data were anonymously recorded to ensure confidentiality. The patients or their legal representtatives signed the Informed Consent. All patients included in the study were in a moderate, severe or critical condition, according to the Cuban national protocol approved by the Ministry of Public Health for COVID-19. The patients were classified according to the following criteria.

Moderately ill patients:

- Fever or cough. Evidence of lower respiratory disease during clinical assessment or imaging. SpO2 ≥94%. Neutrophil-to-lymphocyte ratio (NLR) > 3

Seriously ill patients:

- Fever, cough and polypnea. SpO2 <94 % in room air at sea level, a respiratory rate >30 breaths/min, PaO2/FiO2 <300 mm Hg, or lung infiltrates >50%. NLR > 5

Critically ill patients:

- Acute respiratory distress syndrome (ARDS) evidenced by PaO2/FiO2 ≤ 300 mm Hg.
- Sequential Organ Failure Assessment (SOFA) >2 Bilateral multilobar interstitial pattern < 50% in chest x-rays and CT Sepsis. Septic Shock

The patients also received the standard therapy established in the above-mentioned protocol [23]. They received oxygen therapy or mechanical ventilation, according to their clinical and respiratory condition. This study was conducted following the Helsinki Declaration for research in humans [25] and the guidelines of the International Conference on Harmonization [26]. The Ethics and Scientific Committees of each study site and the Cuban Regulatory Authority (CECMED, http://www.cecmed.cu/) approved the protocol. The study was registered as RPCEC00000313 at the Cuban Clinical Trial Registry (www.registroclinico.sld.cu).

2.2 Design of the study

The information on each patient including sex, clinical classification and comorbidities, laboratory tests and clinical outcomes were obtained from their medical records. Data on safety were collected according to Regulation 45/2007 from the Cuban Regulatory Authority: "Requirements for reporting adverse events in ongoing clinical trials, based on WHO regulations." This regulation conforms to the "National Cancer Institute Common Toxicity Criteria Adverse Event version 3.0" (National Cancer Institute, Frederick, MD, USA).

The peptide was administered intravenously every 12 hours. The dose of CIGB-258 was 1 mg for moderately and seriously ill patients and 2 mg for critically ill patients. Irrespective of their clinical condition, obese patients received 2 mg every 12 hours. Patients were treated until their clinical and radiological conditions were resolved, as evidenced by the decrease in NLR. Figure 1 shows the design of this study.

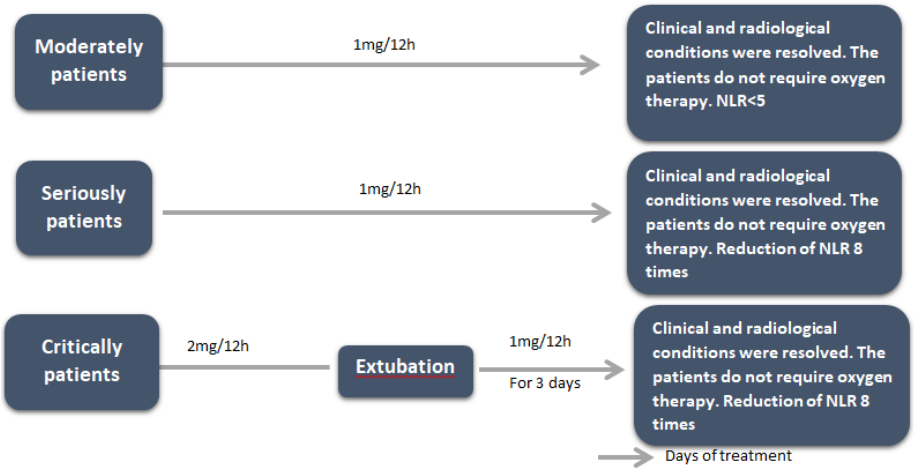

Figure 1: Diagram of CIGB-258 treatment. Moderately ill and seriously ill patients were treated with 1mg of CIGB-258 every 12 h. Critically ill patients were treated with 2 mg of CIGB-258 every 12 h. After extubation, the critically ill patients received 1mg of CIGB-258 daily for another three days. Obese patients received 2 mg every 12 hours, irrespective of their clinical condition. The peptide was administered intravenously. Moderately ill patients were treated until their clinical and radiological conditions were resolved and they did not need oxygen therapy and theirs NLR decreased below 5. The seriously and critically ill patients were treated until their clinical and radiological conditions were resolved and they did not need oxygen therapy and the NLR decreased below 5, compared to the value of this biomarker before starting treatment. NLR: neutrophil-lymphocyte ratio.

2.3 Biomarkers assessments

NLR in peripheral blood, serum values of LDH and CRP were quantified in all patients enrolled in the study before and during the CIGB-258 treatment. A Sysmex automated hematology analyzer was used to carry out blood counts according to the manufacturer's protocol (SysmexPartec, Milan, Italy). Serum samples were analyzed on a fully automated clinical chemistry analyzer (Beckman Olympus, Beckman, Germany), according to the manufacturer's instructions.

2.4 IL-6 assessments

Serum samples were obtained before the CIGB-258 treatment and 96 hours after the first inoculation. IL-6 concentrations in sera were assessed by ELISA (Quantikine®, R&D Systems, USA) according to the recommendations of the manufacturer, with lower limits of quantification of 3.13pg/ mL.

2.5 Statistical analysis

Continuous variables (Table 1) were expressed as median (range) and compared using the Mann-Whitney U test; categorical variables (moderate, severe and critical patients) were expressed as number (%) and compared by the $\chi 2$ test. NLR, LDH, CRP and IL-6 were analyzed using GraphPad Prism version 7.04. (GraphPadSofware, San Diego California, USA). Samples were examined for normality and equal

variance with Kolmogorov-Smirnov and Bartlett's tests, respectively. The Mann-Whitney U test was used for NLR, CPR, LDH, PaO2/FiO2 and SpO2. IL-6 levels were analyzed using the two-way ANOVA and Bonferroni's multiple comparisons test $P<0.05$.

Characteristics	**All patients (n=104)**	**Moderate (n=19, 18.3%)**	**Seriuos (n=63, 60.6%)**	**Critical (n=22, 21.1%)**
Age, mean (range)	61 (23-88)	60 (27-88)	61 (23-87)	59 (42-80)
Sex				
Female	45 (43.3%)	9 (47.4)	28 (44.4%)	8 (36.4%)
Male	59 (56.7%)	10 (52.6%)	35 (55.6%)	14 (63.6%)
Comorbidities				
Arterial Hypertension	66 (73.3%)	13 (86.7%)	40 (71.4%)	13 (68.4%)
Cardiovascular diseases (ischemic heart, thromboembolism, heart failure, peripheral arterial insufficiency, cardiac arrhythmia)	23 (25.6%)	6 (40%)	11 (19.6%)	6 (31.6%)
Diabetes mellitus	26 (28.9%)	5 (33.3%)	15 (26.8%)	6 (31.6%)
Chronic obstructive pulmonary disease	13 (14.4%)	3 (13.3%)	9 (16.1%)	2 (10.5%)
Bronchial asthma	11 (12.2%)	-	9 (16.1%)	2 (10.5%)
Obesity	14 (15.6%)	1 (6.7%)	8 (14.3%)	5 (26.3%)
Malignant tumors	8 (8.9%)	-	5 (8.9%)	3 (15.8%)
Chronic kidney disease	6 (6.7%)	1 (6.7%)	4 (7.1%)	1 (5.3%)
Others (bronchiectasis, gout, cerebrovascular disease, hydrocephalus, AIDS, anemia, liver cirrhosis, Hepatitis virus C)	11 (12.2%)	1 (6.7%)	9 (16.1%)	1 (5.3%)
Patients with two comorbidities	27 (30.0%)	6 (40.0%)	18 (32.1%)	3 (15.8%)
Patients with three or more comorbidities	33 (36.7%)	5 (33.3%)	20 (35.7%)	8 (42.1%)
None	14 (13.5%)	4 (21.1%)	7 (11.1%)	3 (13.6%)
*AIDS: Acquired Immunodeficiency Syndrome				

Table 1: Demographic characteristics of COVID-19 patients treated with CIGB-258.

3. Results

3.1 Demographic characteristics and clinical description of patients

One hundred and four patients with COVID-19 in moderate, serious or critical conditions were included in this study. Demographic characteristics, clinical classification and comorbidities of patients are summarized in Table 1. The median age (min-max) of patients was 61

(23-88) years old. Ninety patients had one or more comorbidities, including hypertension and other cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, bronchial asthma, obesity, cancer and chronic kidney disease. Other diseases found in 12.2% of the patients were: bronchiectasis, gout, cerebrovascular disease, hydrocephalus, AIDS, anemia, liver cirrhosis and hepatitis C. In 30 % of the patients, two comorbidities were present and in 36.7 %, there were more than two comorbidities. Out of 104 patients, only fourteen did not have comorbidities. Nineteen patients were classified as moderately ill, sixty-three as seriously ill and twenty-two as critically ill. Moderately ill patients had a mild respiratory disease shown by clinical and radiological assessment. Ten of these patients did not require any kind of oxygen support and nine patients needed oxygen therapy, including nasal cannula or an oxygen mask (Table 2). Seriously ill patients had fever, cough, fatigue and polypnea as the most common symptoms. Fifty-three were treated with oxygen therapy and only nine patients in this condition did not require oxygen therapy. Although these nine patients had SpO2> 94%, they were classified as severe based on their clinical assessment and comorbidities. One seriously ill patient needed non-invasive mechanical ventilation in the continuous positive airway pressure (CPAP) mode. Before the CIGB-258 treatment, twenty critically ill patients had acute respiratory distress syndrome (ARDS), according to the Berlin criteria [27]. These patients were under mechanical ventilation when starting with CIGB-258. Only two patients in critical conditions did not require mechanical ventilation, one of these patients had hepatic encephalopathy [28] and the other patient had extreme bradycardia due to ischemic heart disease. One critically ill patient received non-invasive ventilation in the CPAP mode (Table 2).

3.2 Therapy outcomes

Out of all patients included in this study, 93.3% recovered from the disease and were discharged from the hospital. The average treatment duration with CIGB-258 was seven and eleven days for moderately and seriously or critically ill patients, respectively (Table 2). All moderately ill patients improved their clinical status, after 96 hours of treatment with CIGB-258. None of these patients progressed to severe disease stages. CRP and LDH decreased significantly (P=0.0014 and P=0.0426 respectively) after seven days of treatment. The NLR decreased below 5, after seven days (Table 3). All moderately ill patients were discharged from the hospital (Table 2). Out of sixty-three seriously ill patients, fifty-two did not progress to a critical condition. These patients expressed a marked improvement in their clinical condition after 96 hours of treatment with CIGB-258. The improvement in functional or radiological respiratory parameters agreed with clinical improvement. On the seventh day, the NLR was less than 5 in most of these patients. CRP decreased significantly (P=0.0151) as compared to the baseline and LDH tended to normalize (Table 3).

	All patients (n=104)	**Moderate (n=19)**	**Seriuos (n=63)**	**Critical (n=22)**
Days treated with CIGB-258	10 (2-35)	7 (4-9)	11(2-35)	11 (6-20)
Oxygen support				
Invasive mechanical ventilation	19 (22.9%)	-	-	19 (95.0%)
Non-invasive ventilation	2 (2.4%)	-	1 (1.9%)	1 (5.0%)
Oxygen therapy	62 (74.7%)	9 (100%)	53 (98.1%)	-
No type of oxygen support required	21 (20.2%)	10 (52.6%)	9 (14.3%)	2 (9.1%)
Clinical outcomes				
Alive, discharged from the hospital	97 (93.3%)	19 (100%)	58 (92.1%)	20 (90.9%)
Death	7 (6.7%)	-	5 (7.9%)	2 (9.1%)

Table 2: Days of treatment with CIGB-258, characteristics of oxygen support and outcomes by clinical stages of patients.

	Reference range	**Moderately ill patients**		**Seriously ill patients**			**Critically ill patients**			
		Before treatment	**Day 7**	**P**	**Before treatment**	**Day 7**	**P**	**Before treatment**	**Day 7**	**P**
Prognostic markers										
NLR	≤ 5	5.1 ± 4.5	2.7 ± 2.3	ns	9.7 ± 8.7	5.5 ± 4.7	ns	12.9 ± 9.31	8.7 ± 4.76	ns
CRP(mg/L)	≤ 5	50 ± 48.7	7 ± 2.7	0.0014	71.8 ± 41.8	33 ± 28	0.0151	158 ± 129	49 ± 34.6	0.033
LDH(U/L)	230-460	584 ± 201	444 ± 89	0.0426	557 ± 257	491± 352	ns	968 ± 379	633 ± 251	ns
Ventilation parameters										
PaO2 / FiO2	>300	480 ± 93	478 ± 64	ns	369 ± 133	413 ± 164	ns	210 ± 73	349 ± 112	0.005
SpO2 (%)	>93	97 ± 1.1	97 ± 1.3	ns	95 ± 9.8	96 ± 15	ns	93 ± 5	97 ± 3	0.0478

NLR: neutrophil-lymphocyte ratio; CRP: C-reactive protein; LDH: lactate dehydrogenase; ns: non-significant difference. Differences were analyzed using the Mann-Whitney test

Table 3: Inflammation biomarkers and ventilation parameters of COVID-19 patients under CIGB-258 Treatment.

Eleven seriously ill patients progressed to the critical phase of the disease. Ten of them had more than one comorbidity and seven were over 70 years of age. Six patients that had progressed to a critical condition

recovered and were discharged from the hospital and five patients died. The patients who died had more than two comorbidities. One of the patients had metastatic prostate cancer. Three patients had chronic obstructive pulmonary disease and two patients had chronic kidney disease (Table 4). Fifty-eight seriously ill patients recovered and were discharged from the hospital (Table 2). Twenty of the critically ill patients recovered from their ARDS and were extubated.

During the treatment with CIGB-258, the patients improved their oxygen uptake efficiency. CRP decreased significantly (P=0.0033) compared to the baseline and LDH tended to normalize by the seventh day of the treatment (Table 3). These patients were discharged from the hospital (Table 2). Two patients from this group died (Table 4). No adverse events associated with CIGB-258 were reported during treatment or in the follow-up stage.

3.3 Effect of CIGB-258 on inflammation biomarkers

Laboratory parameters linked with inflammation including NLR in peripheral blood, LDH and CRP, gradually normalized during the treatment with CIGB-258 (Table 3). Furthermore, quantified IL-6 levels in these patients (moderate, severe and critical conditions) are included in this study. IL-6 was measured in the sera of patients before the treatment and at day four after starting the treatment with CIGB-258. As shown in figure 2, the use of CIGB-258 led to a significant reduction of this cytokine in seriously (P=0.0137) and critically ill patients (P=0.0134). Likewise, IL-6 levels were analyzed independently in moderate, serious, and critically ill patients. The levels of this cytokine were significantly higher (P=0.0154) in critically ill patients than in moderate and seriously ill patients, before the treatment with CIGB-258. However, no significant difference was detected between the three groups at 96 hours after starting the CIGB-258 treatment (Figure 2).

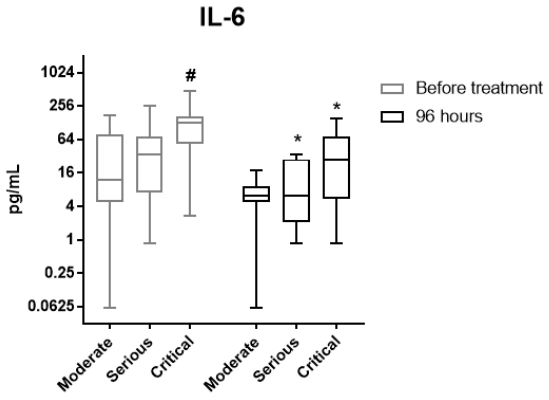

Figure 2: IL-6 levels among clinical states and at 96 hours after CIGB-258 treatment. Data are presented as means ± standard deviation. # represents significant differences between clinical stages. * represents significant differences between times. Serum samples were obtained before treatment (light bars) and at 96 hours (dark bars). Differences were analysed using the two-way ANOVA and Bonferroni's multiple comparisons test. P<0.05.

Case	Clinical classification	Sex	Age	Comorbidities	Clinical outcomes
1	Seriously ill	M	56	Arterial hypertension. Diabetes mellitus. Chronic kidney failure. Prostate cancer	Death
2	Seriously ill	M	84	Arterial hypertension. Diabetes mellitus. Ischemic heart disease. Chronic obstructive pulmonary disease	Death
3	Seriously ill	M	58	Diabetes mellitus. Obesity	Alive, discharged from Hospital
4	Seriously ill	F	54	Chronic lymphoid Leukemia	Alive, discharged from Hospital
5	Seriously ill	M	72	Arterial hypertension. Diabetes mellitus	Alive, discharged from Hospital
6	Seriously ill	M	78	Arterial hypertension. Ischemic heart disease. Chronic obstructive pulmonary disease. Chronic kidney failure	Death
7	Seriously ill	M	85	Arterial hypertension. Ischemic heart disease	Death
8	Seriously ill	F	80	Arterial hypertension. Chronic obstructive pulmonary disease	Death
9	Seriously ill	F	74	Diabetes mellitus. Peripheral arterial insufficiency	Alive, discharged from Hospital
10	Seriously ill	M	58	Arterial hypertension. Diabetes mellitus. Deep vein thrombosis. Obesity	Alive, discharged from Hospital
11	Seriously ill	M	75	Arterial hypertension. Ischemic cerebrovascular disease. Operated hip fracture	Alive, discharged from Hospital
12	Critically ill	M	53	Arterial hypertension. Schizophrenia. Malnutrition	Death
13	Critically ill	F	65	Arterial hypertension. Chronic obstructive pulmonary disease. Obesity	Death

Table 4: Demographic characteristics of COVID-19 patients treated with CIGB-258, in which inflammation progresses

4. Discussion

The pathophysiology of COVID-19 is highly multifaceted but three stages associated with severity can be described. Stage I is associated with early infection, which is characterized by symptoms of upper respiratory tract infection and stage II is the pulmonary phase when the patients progress to full-blown pneumonia. The last phase corresponds to hyperinflammation, when patients develop ARDS, sepsis and multiple organ failures [29]. Anti-inflammatory therapies for autoimmune diseases are under consideration for the control of this hyperinflammation. These therapies include monoclonal antibo-

dies against proinflammatory cytokines such as IL-1 (Anakinra) and IL-6 (Tocilizumab) [30, 31]. Other alternatives are Bruton kinase inhibitors and Janus kinase inhibitors [32, 33]. These drugs may reduce hyperinflammation, but will cause immunosuppression. However, immunosuppression is not beneficial in the course of viral infections; on the contrary, in this condition a robust immune response is needed to eliminate the virus.

CIGB-258 has shown, in previous studies, that it can inhibit hyperinflammation, in severe phases of COVID-19, while the patients treated with CIGB-258 did not show symptoms of possible immunosuppression associated with the drug. This treatment restores the NLR and produces a favorable outcome for the patients [20, 21]. Here, the treatment with CIGB-258 was applied to cohorts of patients in different stages of inflammation. The patients were classified as moderate, severe and critical, according to the Cuban classification criteria for COVID-19 patients, which are in line with the WHO criteria. Similar to previous reports, signs of immunesuppression and adverse effects associated with CIGB-258 were not detected in this study. Most patients included in this study had comorbidities and many of them had two or more of these pathological conditions that complicate the course of COVID-19. Many authors have described that arterial hypertension, cardiovascular diseases, diabetes mellitus, obesity, and others, affect the progression towards the severe phases of COVID-19 [9, 34,35]. In this study, the percentages of patients with comorbidities were similar in the three groups.

The patients who progress toward a severe phase of COVID-19 gradually increase biomarkers of inflamemation, such as CRP, LDH and NLR. The increases in CRP concentrations have been linked to an unfavorable development of COVID-19 disease [6, 9]. LDH is considered a good biomarker associated with the progression of COVID-19 pneumonia [10]. The NLR has been widely used as a severity predictor for COVID-19 [36]. Additionally, patients who progress towards the severe phases of COVID-19 gradually increase the levels of pro-inflammatory cytokines such as IL-6 [37]. All patients classified as moderate in this study had increased levels of NLR, CRP and LDH. Also, their clinical and radiological assessment indicated that these patients were progressing to the hyperinflammation phase. These criteria were the basis for starting the CIGB-258 treatment. CRP and LDH were significantly reduced, and the NLR decreased below 5, after seven days of treatment. The reduction in these biomarkers was in agreement with the clinical improvement of the patients. Besides, IL-6 levels tended to decrease after 96 hours of treatment. None of the patients with a moderate classification in this study progressed to the serious stages of the disease. This outcome is very interesting since it reinforces the therapeutic potential of CIGB-258. The result indicates that CIGB-258 prevents the progression to the severe phase in COVID-19 patients. These results contrast with other drugs used in patients with moderate COVID-19 such as dexamethasone. The recovery trials showed no benefit with dexamethasone in moderately ill patients not requiring oxygen. Moreover, the use of dexame-thasone can be harmful for these patients [38].

In this study, fifty-two seriously ill patients did not progress to the critical condition. These patients improved and the inflammation biomarkers diminished. Consequently, IL-6 levels significantly decreased after 96 hours of the treatment. High systemic concentrations

of IL-6 have been correlated with disease severity [7]. These results are similar to our previous reports, in which TNF and IL-10 also decreased [20, 21]. Out of sixty-three seriously ill patients, only eleven patients progressed to a critical condition. These patients had several comorbidities that worsened their clinical condition. Despite this, six of these patients recovered from their critical condition and were discharged from the hospital. Twenty critically ill patients under treatment showed clinical improvement, which was associated with a normalization of CRP and LDH. Notably, a decrease in circulating IL-6 was found in these patients. In this study, IL-6 levels were higher in critically ill patients than in moderate and seriously ill patients. IL-6 has been involved in the progression of several viral infections [39]. During CIGB-258 treatment, IL-6 levels were significantly reduced, indicating the decline in inflammation. Out of twenty-two critically ill patients, two died. Both patients had several comorbidities that hampered their recovery.

The results presented in this study indicate that the early administration of CIGB-258 can improve the condition of moderately ill patients and avoid their progression to severe stages. This effect is in line with the molecular mechanism of this peptide. CIGB-258 inhibits the activity of monocytes, macrophages and neutrophils. This inhibition contributes to the restoration of normal levels of neutrophils and lymphocytes. Also, CIGB-258 has the ability to increase the frequency of Treg [21]. These facts contribute to the resolution of hyperinflammation and the positive outcome of the patients. The main limitation of this study is the lack of a concurrent placebo-control group. The assessment of the efficacy of the CIGB-258 treatment will need randomized, placebo-controlled trials. Nevertheless, the current study ratifies that this peptide can reduce hyperinflammation. These results indicate the therapeutic potential of CIGB-258 and sustain the rationale for additional research on this drug for the treatment of hyperinflammation in other diseases.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the

paper.

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