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CIGB-258 Immunomodulatory Peptide: Compassionate Use for Critical and Severe COVID-19 Patients

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Abstract

CIGB-258 is an immunomodulatory peptide with anti-inflammatory properties derived from Cellular Stress Protein 60 (HSP60). We report the compassionate use of CIGB-258 for patients with COVID-19 in critical or severe conditions. The results presented herein depict the first data of CIGB-258 clinical application in COVID-19 patients.

Sixteen patients with COVID-19 in serious (31%) or critical (69%) conditions were included in this report. All critically ill patients were under invasive mechanical ventilation at CIGB-258 treatment start, and received intravenous administration of 1 mg or 2 mg of CIGB-258 every 12 hours until extubation, followed by 1 mg daily for another three days of treatment. Seriously ill patients were treated with oxygen therapy, including nasal cannula or oxygen mask, and received 1 mg of CIGB-258 every 24 hours, until respiration parameters improvement. The peptide was administered intravenously. Patients in the study were included from March 31 to April 22, 2020.

CIGB-258 showed a favorable clinical safety profile. All critically ill patients recovered from the respiratory distress condition and were extubated. Two of these patients had a fatal outcome due to nosocomial infections. All seriously ill patients considerably improved. Levels of biomarkers associated with hyperinflammation and Interleukin (*IL-6*), *IL-10* and Tumor Necrosis Factor (TNFα) significantly decreased during treatment. Assessment of efficacy will require continuing the randomized, placebo-controlled trials of the CIGB-258 treatment.

Keywords: COVID-19; Hyperinflammation; Cytokine Storm; HSP60; CIGB-258

Abbreviations

HSP60: Cellular Stress Protein 60; *IL*: Interleukin; TNFα: Tumor Necrosis Factor; RA: Rheumatoid Arthritis; Treg: regulatory T cells; PBMCs: Peripheral Blood Mononuclear Cells; NETosis: Neutrophil Extracellular Traps; CECMED: Cuban Regulatory Authority; ARDS: Acute Respiratory Distress Syndrome; CRP: C Reactive Protein; WBC: White Blood Cell Count; LDH: Lactate Dehydrogenase

Introduction

A certain proportion of COVID-19 patients reach the severe phase of the disease, characterized by hyperinflammation [1]. This hyperinflammation is mediated by high levels of proinflammatory cytokines [2]. During this cytokine storm, patients may have cardiovascular collapse, multiple organ failure, and may die [3].

In this context, approved anti-inflammatory therapies for autoimmune diseases are being considered to control this hyperinflammation and reduce mortality in COVID-19 patients. These potential treatments include monoclonal antibodies for *IL-1* (Anakinra) and *IL-6* (Tocilizumab), Bruton kinase inhibitors and Janus kinase inhibitors [4-7]. These treatments may reduce hyperinflammation, but will undoubtedly cause immunosuppression. However, immunosuppression is contra-indicated when there is a viral infection, invoking a possible viral outbreak.

Alternate strategies are being intensively assessed. Among them, CIGB-258 (previously called APL1 or CIGB-814 and hereafter CIGB-258) is an immunoregulatory peptide derived from the human heat shock protein (HSP)60. HSP60 levels increase during viral infections and inflammation. Peptides derived from HSP60 may represent danger signals that can trigger physiological inflammatory responses. Notably, peptides also derived from HSP60 can induce T cells with regulatory function [8].

CIGB-258 induced regulatory effects that have been associated with the inhibition of inflammation in several experimental inflammatory models and in patients with Rheumatoid Arthritis (RA) [9-12].

The molecular mechanism of CIGB-258 in preclinical studies has been associated with an increase of regulatory T cells (Treg) and a decrease of TNF-α and *IL-17*, but without decreasing the percentage of T effector cells, suggesting a decrease of chronic inflammation related to the regulation of the immune system [9,10,13].

A Phase I Clinical Trial with this peptide was carried out in 20 moderately active RA patients. Patients showed decreases in their clinical scores. CIGB-258 treatment led to a significant reduction in levels of interferon-gamma (IFN-γ) and *IL-17* [11]. Moreover, the CIGB-258 treatment induced a significant reduction autoantibody against cyclic citrullinated peptides [12]. A phase II clinical trial in

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RA patients is in progress, where 187 patients have been included.

Phase I and II clinical trials have shown that the treatment with CIGB-258 is safe [11,12]. Furthermore, patients in this clinical study did not have signs or symptoms, which could be interpreted as immunosuppression, during the therapy and the follow-up stage.

Recently, we studied the effect of the CIGB-258 treatment on Peripheral Blood Mononuclear Cells (PBMCs) isolated from RA patients, using proteomic tools. These results suggest that CIGB-258 could act on the activity of monocytes, macrophages and neutrophils. Interestingly, the main biological pathway that may be linked to the molecular mechanism of CIGB-258 activity, is Neutrophil Extracellular Traps (NETosis) (results sent to publish).

Altogether, these findings indicate that CIGB-258 inhibits inflammation without causing immunosuppression. Accordingly, we received approval from the Cuban Regulatory Authority (CECMED, http://www.cecmed.cu/) to initiate CIGB-258 treatment for critically or seriously ill COVID-19 patients.

In this study, we describe the outcomes of a cohort of critical and severe COVID-19 patients treated with CIGB-258 on a compassionate-use basis.

Materials and Methods

Patients

Patients were recruited for the study between March 31 and April 22, 2020, from the Luis Diaz Soto and Pedro Kouri Hospitals in Havana, Cuba. All patient data were anonymously recorded to ensure confidentiality.

This study was conducted according to the Helsinki Declaration for research in humans [14] and the International Conference of Harmonization guidelines. The Ethics and Scientific Committees of each study site and the Cuban Regulatory Authority (CECMED, http://www.cecmed.cu/) approved the protocol. Patients or their legal representatives signed an informed consent before the administration of CIGB-258.

Patients with COVID-19 were diagnosed with severe disease or in critical condition according to the protocol of the Ministry of Public Health of the Republic of Cuba (http://infomed.sld.cu/anuncio/2020/05/11/ministerio-de-salud-publica-protocolo-de-actuacion-nacional-para-la-COVID-19). All patients also received the standard therapy according to the above cited protocol. This compassionate study was registered as RPCEC00000313 at the Cuban Clinical Trial Registry (www.registroclinico.sld.cu).

Procedures

For each study case, sex, clinical classification (severe disease or critical condition) and co-morbidities were recorded. Laboratory tests, chest x-rays and clinical outcomes were obtained from medical records.

The ratio of the arterial partial oxygen pressure to the fraction of inhaled oxygen (PaO_2/FiO_2) was computed for all critically ill patients.

CIGB-258 treatment consisted of 1 mg every 12 hours for critically ill patients. The dose was increased to 2 mg every 12 hours for patients who did not show clinical and radiological improvement in 72 hours. After extubation, the patients received 1 mg of CIGB-258 daily for another three days. Seriously ill patients were treated with 1mg of CIGB-258 every 24 hours, until they resolved their serious clinical condition. The peptide was administered intravenously.

Serum samples were obtained before the CIGB-258 treatment (T0) and after 24 hours, 48 hours, 72 hours and 96 hours. C Reactive Protein (CRP) levels were considered elevated when they were > 5.0 mg/L.

Serum *IL-6*, TNFα, and *IL-10* were measured using the Human CD8+ T-Cell Magnetic Bead Panel (HCD8MAG15K17PMX, EMD Millipore, Germany) according to the manufacturer's instructions. Results were obtained through the Luminex® analyzer and processed in the Milliplex Analyst software v 5.1.0.0 (MAGPIX® and Millipex EMD Millipore, Germany).

Safety

Patients´ safety data 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 with the "National Cancer Institute Common Toxicity Criteria Adverse Event version 3.0" (National Cancer Institute, Frederick, MD, USA).

Statistical analysis

All patients receiving CIGB-258 were included in the clinical, radiological, laboratory and safety assessments. Adverse events, vital signs, chest X-rays and evidence of therapeutic effects were descriptively compared between baseline (T0) and data collected from patients after starting CIGB-258 treatment with no formal statistical tests.

Spearman's rank correlations were used to examine the associations between PaO_2/FiO_2 and CRP.

Laboratory parameters, serum CRP, *IL-6*, TNFα and *IL-10* levels were analyzed using GraphPad Prism version 8.02 (Graph Pad Software, San Diego California, USA). Samples were examined for normality and equal variance with Kolmogorov-Smirnov and Bartlett's tests, respectively. CRP levels were expressed as means, and differences were analyzed with ANOVA and Tukey's post hoc test. Kruskal-Wallis and Dunn post hoc test were used for laboratory parameters. Wilcoxon matched-pair signed rank test was used for serum cytokine levels. P values < 0.05 were considered statistically significant.

Results and Discussion

Baseline Characteristics and Clinical Description of Patients

Sixteen patients with COVID-19 in serious or critical conditions were treated with CIGB-258. Demographic characteristics of patients, their clinical classification and comorbidities are summarized in Table 1. Five (31%) patients were seriously ill, and eleven (69%) patients, critically ill. All critically ill patients were under invasive mechanical ventilation when starting the CIGB-258 treatment. Seriously ill patients had dyspnea, fever and fatigue. These patients were treated with oxygen therapy, including nasal cannula or oxygen mask.

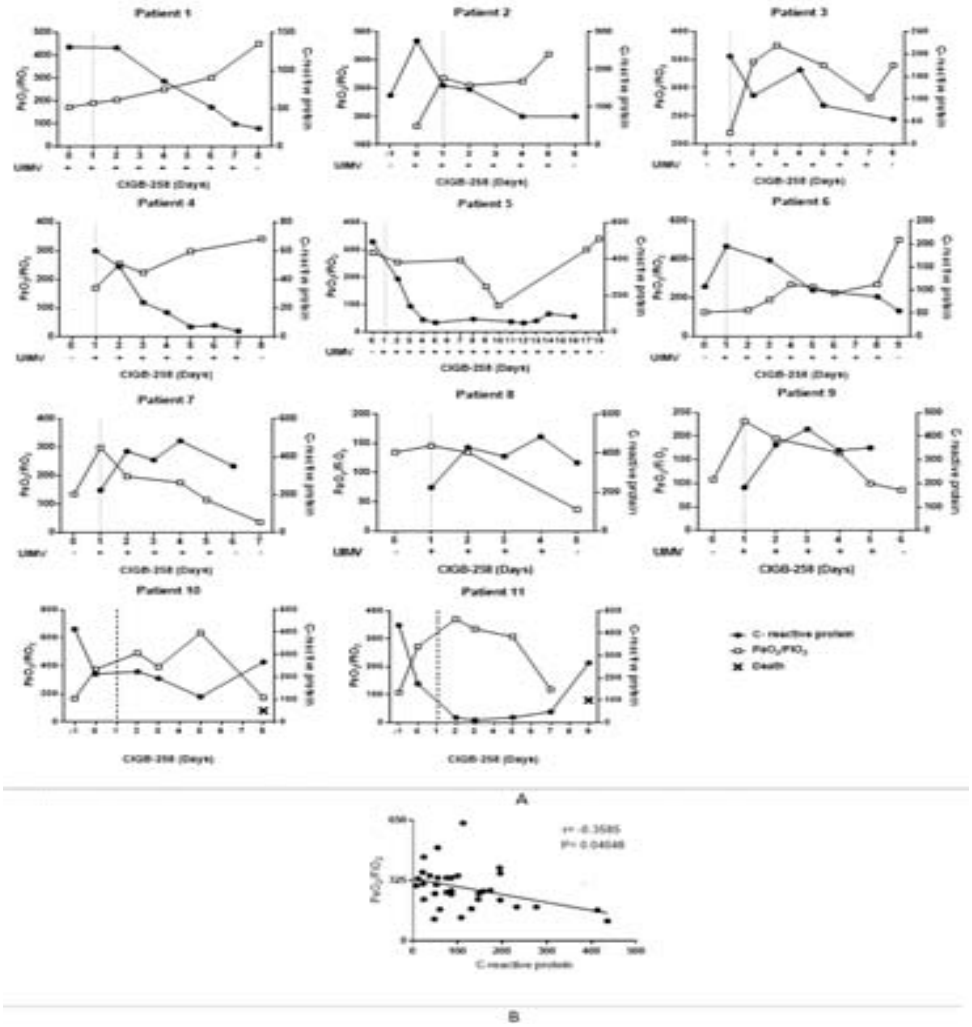

Figure 1: (A) Ratio of the arterial partial pressure of oxygen vs fraction of inspired oxygen (PaO2/FiO2) and C-reactive protein (CRP in mg/L) is shows for all critically ill patients. +: days under invasive mechanical ventilation. Dotted lines: start of CIGB-258 treatment. (B) Correlation between PaO2/FiO2 and CPR levels treatment. The analysis was performed using a Spearman correlation test. (*) means correlation ($p<0.05$).

The median age (min-max) of patients was 61 (19 to 91) years old. Thirteen patients had one or more comorbidities, including: hypertension, diabetes, obesity, bronchial asthma, ischemic heart disease, and cancer. No adverse events associated with CIGB-258 were reported during therapy or in the follow-up stage. Prior to discharge, all patients underwent a CT scan and no lesions associated with fibrotic events were found in their lungs.

Therapy Outcomes

Nine critically ill patients were treated with 1mg of CIGB-258 every 12 hours and two patients were treated with 2 mg every 12 hours (Table 1). Before the CIGB-258 treatment, all critically ill patients had Acute Respiratory Distress Syndrome (ARDS) evidenced by PaO2/FiO2 ≤ 300 mm Hg, according to the Berlin criteria [15]. All critically ill patients recovered from their ARDS and were extubated. Except for patient 5 who was mechanically ventilated for 16 days, the average time for critical patients with mechanical ventilation was of 5 days. Patient 5 had far more comorbidities.

During therapy with CIGB-258, the patients improved their oxygen uptake efficiency and their CPR levels gradually decreased, as shown in Figure 1A. Wan reported that CRP levels were positively correlated with lung lesions and could reflect COVID-19 disease severity [16].

Here, CRP levels were inversely associated with oxygen uptake efficiency in the mechanical ventilation cohort ($P<0.040$) (Figure 1B).

Once extubated, the patients remained on therapy with CIGB-258 for another 72 hours. Two patients died from nosocomial infections. Eight patients were discharged from the hospital an average of ten days after they received the CIGB-258 treatment. One patient remained in an open ward at the time of this report.

Clinical and gasometric improvement was corroborated by radiology. Representative chest X-ray images (patient 2) are shown in Figure 2. The image before the treatment with CIGB-258 is typical of ARDS. This chest X-ray image shows opacity in both hemithoraces with bilateral perihilar infiltrate (Figure 2A). Radiological improvement is observed after 48 hours of treatment with CIGB-258; this image only shows small reticular lesions in the right lung base (Figure 2B). ARDS

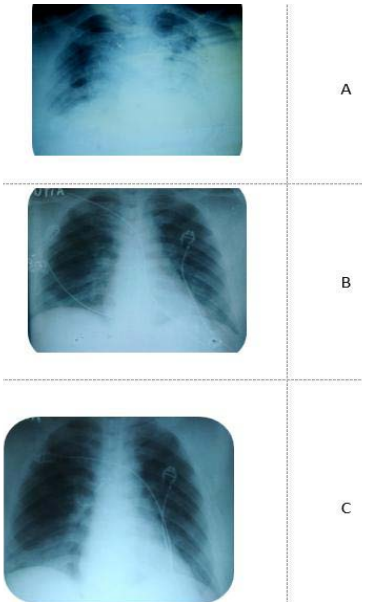

Figure 2: Progress of thorax X-ray imaging of acute respiratory distress syndrome in a representative patient.
A: Thorax X-ray before mechanical ventilation: Opacity of both hemithorax. Right hemithorax with a heterogeneous appearance. Left hemithorax in mass with bilateral perihilar infiltrate. Widening of mediastinum with a vascular appearance.
B: Thorax X-ray after 48 hours of CIGB-258 therapy: Increased bronchovascular markings. Small reticular lesions in the right lung base. Cardiothoracic Ratio (CTR) in the upper normal limit.
C: Thorax X-ray before extubation: Improvement of thorax X-ray imaging with increased bronchovascular bundles.

was resolved during the treatment. This radiological improvement is evidenced in Figure 2C.

Seriously ill patients were treated with 1 mg of CIGB-258 every 24 hours. These patients expressed a marked improvement in their clinical condition after 48 hours of treatment with CIGB-258. Fever disappeared and they no longer required oxygen supplementation. These results indicate that CIGB-258 treatment may inhibit progression to the critical state. Seriously ill patients were discharged from the hospital an average of seven days after they received the treatment with CIGB-258.

Therapy Outcomes correspond with the rapid pharmacokinetic and biodistribution properties of CIGB-258. The maximum blood concentration of CIGB-258, in adult rats, is achieved within 30 minutes to 60 minutes of intravenous administration and the $t^{1/2}$ is 6 hours. Furthermore, the peptide had a wide biodistribution. CIGB-258 targets multiple organs including the lungs [17]. Monocytes, macrophages and neutrophils are involved in the pathogenesis of lung respiratory distress. These cells secrete molecules that mediate inflammation [18].

The Effect of the CIGB-258 Treatment on Laboratory Parameters

Laboratory tests associated with hyperinflammation included White Blood Cell Count (WBC) with differential, metabolic panel, ferritin and Lactate Dehydrogenase (LDH), which were gradually normalized (Table 2).

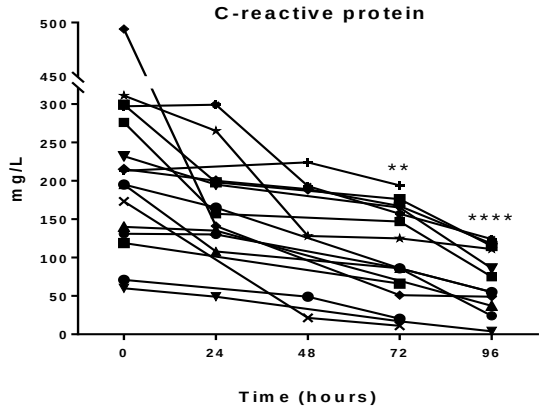

Figure 3: Effect of CIGB-258 on C-reactive protein (CRP) levels for all patients (seriously and critically ill patients). Serum samples were obtained before treatment (0) and at 24 hours, 48 hours, 72 hours and 96 hours. Differences were analyzed using ANOVA and Tukey's post-test (**P<0.001; **** P<0.0001).

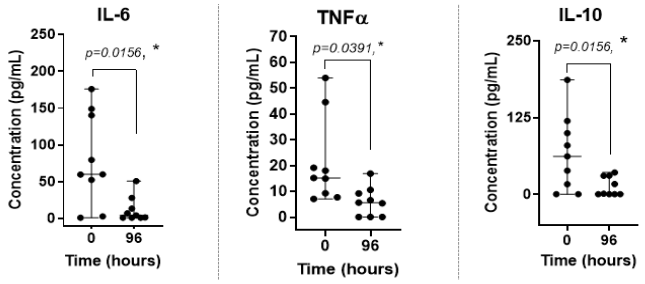

Figure 4: Effect of CIGB-258 on *IL-6*, TNFα and *IL-10* levels. Serum samples were obtained before treatment (0) and at 96 hours. Differences were analyzed using Wilcoxon matched-pair signed rank test (*P<0.05).

CRP kinetics is shown in Figure 3. CRP levels decreased significantly during the treatment with CIGB-258 in all patients (those seriously and critically ill).

IL-6, TNF α and *IL-10* levels were studied in all critically ill patients included in this study. As shown in Figure 4, therapy with CIGB-258 led to a significant reduction of these cytokines. These cytokines are linked with the cytokine storm [19].

Furthermore, patients in this cohort had lymphopenia. Lymphopenia seems to correlate with serum *IL-6*, *IL-10*, and TNF-α [20]. These cytokines decreased and lymphocyte levels gradually normalize during CIGB-258 treatment. These findings suggest that CIGB-258 treatment may control cytokine storm in these patients.

In a report by Li et al, where they characterized PBMC proteomic profile in mild and severe COVID-19 cases, Non-Structure Protein (NSP) and NSP10 were identified as potential virulence factors for SARS-CoV-2. These proteins interact with NF-Kappa-B-Repressing Factor (NKRF) to facilitate *IL-8*/*IL-6* induction, leading to a profound influx and activation of neutrophils into infected lungs [21]. According to our proteomic study, CIGB-258 treatment may interfere with the activation of neutrophils and alveolar macrophages. This fact could also contribute to reduction of cytokine levels described in the present study [22,23].

Table 1: Demographic characteristics of COVID-19 patients treated with CIGB-258 and results of the therapy.

Case No.	Age	Sex	Clinical classification	Comorbidities	Clinical outcomes
1	70	M	Critically ill	Cardiac arrhythmia	Alive, discharged from Hospital
2	42	M	Critically ill	Hypertension, Diabetes, Obesity	Alive, discharged from Hospital
3	55	M	Critically ill	None	Alive, discharged from Hospital
4	64	F	Critically ill	Hypertension	Alive, discharge from Hospital
5[a]	42	F	Critically ill	Adrenal gland tumor, Diabetes, Obesity, Cushing's syndrome, Multiple thyroid nodules	Alive, discharge from ICU
6[a]	78	M	Critically ill	Bladder cancer, Diabetes	Alive, discharged from Hospital
7	49	M	Critically ill	None	Alive, discharged from Hospital
8	80	M	Critical ill	Hypertension, Bronchial asthma, Ischemic heart disease	Alive, discharged from Hospital
9	60	M	Critically ill	Hypertension, Obesity, Bronchial asthma	Alive, discharged from Hospital
10	87	M	Critically ill	Bronchial asthma	Death
11	68	F	Critically ill	Hypertension	Death
12	19	M	Seriously ill	None	Alive, discharged from Hospital
13	76	M	Seriously ill	Hypertension, Diabetes, Ischemic heart disease	Alive, discharged from Hospital
14	91	F	Seriously ill	Diabetes, Ischemic heart disease	Alive, discharged from Hospital
15	45	F	Seriously ill	Glomerulopathy	Alive, discharged from Hospital
16	55	M	Seriously ill	Hypertension	Alive, discharged

a: Dose of CIGB-258: 2mg/12 hours; M: Male; F: Female; ICU: Intensive Care Unit

Table 2: Laboratory test of COVID-19 positive patients under CIGB-258 treatment.

Count Blood cell	Reference range	Before treatment median (range)	CIGB- 258 treatment median (range) Day 2	Day 4	End of therapy
White blood cell (10^9/L)	04-11	8.5 (3.1-15.7)	10.6 (4.6-24)	13.0 (8.3-21)	10.7 (4.2 - 17) **
Platelet count (10^9/L)	150 - 450	286 (172- 406)	317 (189-507)	315 (168 – 570)	266 (93- 397)
Neutrophils (%)	50- 70	79 (53-98)	82 (71-92)	80 (46-89)	75 (68.8 – 87)
Lymphocyte (%)	20 - 40	11.8 (9 - 16)	10.1 (4.2- 14)	8.7 (5.2- 22)	16.4 (11- 24)
Metabolic Panel					
Creatinine (µmol/L)	47- 125	109 (66- 199)	99 (64- 186)	110 (69- 178)	68.9 (59 -98) **
Alkaline Phosphatase (U/L)	100- 290	189 (143 - 250)	178 (139 - 260)	178 (145 - 235)	140 (82 - 191)
Lactate (mmol/L)	0.4 – 2.0	1.85 (1 - 2.3)	1.48 (1 - 1.9)	1.64 (1 - 1.9)	1.74 (1 -2.4)
Prognostic Markers					
LDH (U/L)	230 - 460	1245 (596- 3678)	660 (485- 896)	825 (499- 1130)	463 (312- 621) **
Ferritin (ng/mL)	12.5 – 350	1295 (710 – 1768)	976 (45- 1617)	943 (64- 1500)	387 (78 - 630) **
Coagulation parameters					
Prothrombin time (seg.)	14-15	14. 8 (14- 17)	15.8 (14- 18)	15.25 (15- 17)	14 (13- 15)
Activated partial thromboplastin time (seg)	21 - 40	30 (25- 39)	32 (23- 40)	31 (23- 40)	27.8 (22 -37)
Fibrinogen (g/L)	02-4	3 (2.8- 3.7)	3.1 (2.2- 3.6)	2.8(1.2-3.4)	2.3 (1.1 – 3.9)

Differences were analyzed using Kruskal-Wallis and Dunn post hoc test (*P<0.05, **P<0.005)

Conclusion

In this cohort of critical and severe COVID-19 patients treated with compassionate-use CIGB-258, clinical improvement was observed in all patients.

The main limitation of this exploratory and compassionate study is the absence of data from a cohort of similar COVID-19 cases not treated with CIGB-258.

Nevertheless, our findings show that the treatment of COVID-19 cases with CIGB-258, was associated with a concomitant decrease in lung inflammation and circulating levels of CRP, ferritin, LDH and creatinine. These preliminary results are encouraging and suggest that CIGB-258 may exert a wide spectrum of activities to limit the inflammatory cascade in the lungs of COVID-19 cases.

In critically ill patients, gasometric parameters improved during the therapy with our peptide, which was associated with a normalization of CRP and others inflammatory markers. Notably, we saw a decrease in circulating *IL-6*, TNF-α and *IL-10* levels that accompanied CIGB-258 treatment. These results suggest that CIGB-258 treatment was able to abolish cytokine storm in these patients.

The oxygenation and clinical conditions of seriously ill patients on supplemental oxygen, improved quite rapidly on starting with CIGB-258. These patients did not require oxygen therapy after the first 24 hours of treatment with CIGB-258. Hence, the early administration of CIGB-258 may improve the condition of seriously ill patients and avoid their evolution to the critical stage.

Probably, therapeutic effect of CIGB-258 in critical and severe COVID-19 patients is associated with the expansion of Treg. In preclinical studies we have found evidence that CIGB-258 increases Treg levels. Two studies observed reduced frequencies of Treg cells in severe COVID-19 cases. Treg limit T cell activation, thereby effectively reducing the levels of pro-inflammatory cytokines associated with the cytokine storm in COVID-19 patients.

Therapy with CIGB-258 was well tolerated in all patients. Patients discharged from the hospital are under strict pharmaco-surveillance. CIGB-258 is currently being used in other Cuban hospitals for the treatment of seriously and critically ill COVID-19 patients. Assessment of efficacy will require ongoing the randomized, placebo-controlled trials of the CIGB-258 therapy.

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Study Registration: RPCEC00000313.

References

1. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
3. Mehta P, McAuley DF, Brown M, Sanchez E, Rachel S, Tattersall R, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
4. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020;2(7):e393-400.
5. Capraa R, DeRossia N, Mattiolib F, Romanelli G, Scarpazza C, Sormani M, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31-5.
6. Roschewski M, Lionakis MS, Sharman JP, Roswarski J, Goy A, Monticelli MA, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. Sci Immunol. 2020;5:48.
7. Peterson D, Damsky W, King B. The use of Janus kinase inhibitors in the time of SARS-CoV-2. J Am Acad Dermatol. 2020;82(6):e223-6.
8. van Eden W, van der Zee R, Prakken B. Heat-shock proteins induce T-cell regulation of chronic inflammation. Nat Rev Immunol. 2005;5(4):318-30.
9. Domínguez MC, Lorenzo N, Barberá A, Darrasse-Jeze G, Hernandez MV, Torres AM, et al. An altered peptide ligand corresponding to a novel epitope from heat-shock protein 60 induces regulatory T cells and suppresses pathogenic response in an animal model of adjuvant induced arthritis. Autoimmunity. 2011;44(6):471-82.
10. Lorenzo N, Altruda F, Silengo L, Dominguez MC. APL-1, an altered peptide ligand derived from heat-shock protein, alone or combined with methotrexate attenuates murine collagen induced arthritis. Clin Exp Med. 2017; 17(2):209-16.
11. Prada D, Gómez J, Lorenzo N, Corrales O, López A, González E, et al. Phase I clinical trial with a novel altered peptide ligand derived from human heat-shock protein 60 for treatment of rheumatoid arthritis: safety, pharmacokinetics and preliminary therapeutic effects. Journal of Clinical Trials. 2018;8(339):2167-0870.
12. Corrales O, Hernández L, Prada D, Gómez J, Reyes Y, López AM, et al. CIGB-814, an altered peptide ligand derived from human heat-shock protein 60, decreases anti-cyclic citrullinated peptides antibodies in patients with rheumatoid arthritis. Clin Rheumatol. 2019;38(3):955-60.
13. Barberá A, Lorenzo N, van Kooten P, van Roon J, de Jager W, Prada D, et al. APL1, an altered peptide ligand derived from human heat-shock protein 60, increases the frequency of Tregs and its suppressive capacity against antigen responding effector CD4+T cells from rheumatoid arthritis patients. Cell Stress Chaperones. 2016; 21(4):735-44.
14. World Medical Association. World medical declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Med Assoc. 2013;310(20):2191-4.
15. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson N, Caldwell E, Fan Eet al. Acute respiratory distress syndrome: The Berlin definition. JAMA. 2012;307(23):2526-33.
16. Wan L. CRP levels were positively correlated with lung lesions and reflected disease severity. Med Mal Infect. 2020;50(4):332-4.
17. Domínguez MC, Cabrales A, Lorenzo N, Padrón G, Gonzalez LJ. Biodistribution and pharmacokinetic profiles of an Altered Peptide Ligand derived from Heat-shock proteins 60 in Lewis rats. Cell Stress and Chaperones. 2020;25(1):133-40.
18. Bendib I, Chaisemartin l, Granger V, Schlemmer F, Maitre B, Sophie H, et al. Neutrophil extracellular traps are elevated in patients with pneumonia related acute respiratory distress syndrome. Anesthesiology.2019;130(4):581-91.
19. Gong J, Dong H, Xia Q, Huang YZ, Wang D, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. Preprint from Med Rxiv. 2020.
20. Diao B, Wang C, Tan Y, Chen X, Ying L, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020; 11: 827.
21. Li J, Guo M, Tian X, Zhang S, Yang S, Tao Y, et al. Virus-host interactome and proteomic survey of PMBCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis. Med (N Y). 2020.
22. Chen G, Wu D, Guo W, Liu C, Wang X, Wang T, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-9.
23. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8.