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Article

Treatment with an Anti-CK2 Synthetic Peptide Improves Clinical Response in COVID-19 Patients with Pneumonia. A Randomized and Controlled Clinical Trial

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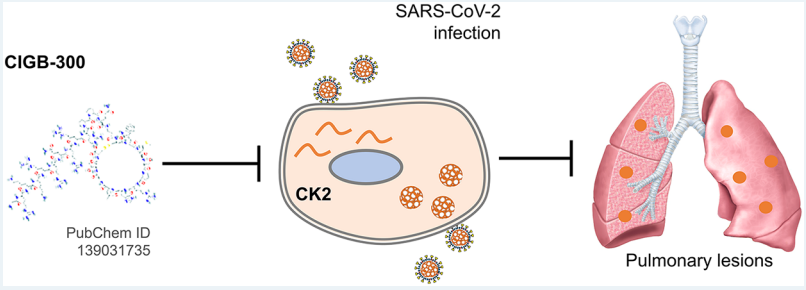

ABSTRACT: The instrumental role of CK2 in the SARS-CoV-2 infection has pointed out this protein kinase as promising therapeutic target in COVID-19. Anti-SARS-CoV-2 activity has been reported by CK2 inhibitors *in vitro*; however, no anti-CK2 clinical approach has been investigated in COVID-19. This trial aimed to explore the safety and putative clinical benefit of CIGB-325, an anti-CK2 peptide previously assessed in cancer patients. A monocentric, controlled, and therapeutic exploratory trial of intravenous CIGB-325 in adults hospitalized with COVID-19 was performed. Twenty patients were randomly assigned to receive CIGB-325 (2.5 mg/kg/day during 5-consecutive days) plus standard-of-care (10 patients) or standard-of-care alone (10 patients). Adverse events were classified by the WHO Adverse Reaction Terminology. Parametric and nonparametric statistical analyses were performed according to the type of variable. Considering the small sample size, differences between groups were estimated by Bayesian analysis. CIGB-325 induced transient mild and/or moderate adverse events such as pruritus, flushing, and rash in some patients. Both therapeutic regimens were similar with respect to SARS-CoV-2 clearance in nasopharynx swabs over time. However, CIGB-325 significantly reduced the median number of pulmonary lesions (9.5 to 5.5, $p = 0.042$) at day 7 and the proportion of patients with such an effect was also higher according to Bayesian analysis (pDif > 0; 0.951). Also, CIGB-325 significantly reduced the CPK ($p = 0.007$) and LDH ($p = 0.028$) plasma levels at day 7. Our preliminary findings suggest that this anti-CK2 clinical approach could be combined with standard-of-care in COVID-19 in larger studies.

KEYWORDS: *COVID-19, SARS-CoV-2, protein kinase CK2, CIGB-325*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and has infected nearly 20 million people.[1,2] Many infected people are asymptomatic or experience mild symptoms and recover without medical intervention.[3,4] However, older people and those with comorbid hypertension, diabetes, obesity, and heart disease are at higher risk of life-threatening illness.[5,6] Therefore, development of an effective antiviral drug for COVID-19 is a global health priority. Along with the development of new antiviral drugs, repurposing existing drugs for COVID-19 treatment is also accelerated.[7] Some antiviral drugs have shown high efficacy against SARS-CoV-2 both *in vitro*[8] and *in vivo*.[9,10] A number of clinical studies such as compassionate use programs and clinical trials have been conducted to test the efficacy of FDA-approved drugs, such as lopinavir and ritonavir, chloroquine, favipiravir, and remdesivir (RDV).[11−14] More recently, a double-blind, randomized,

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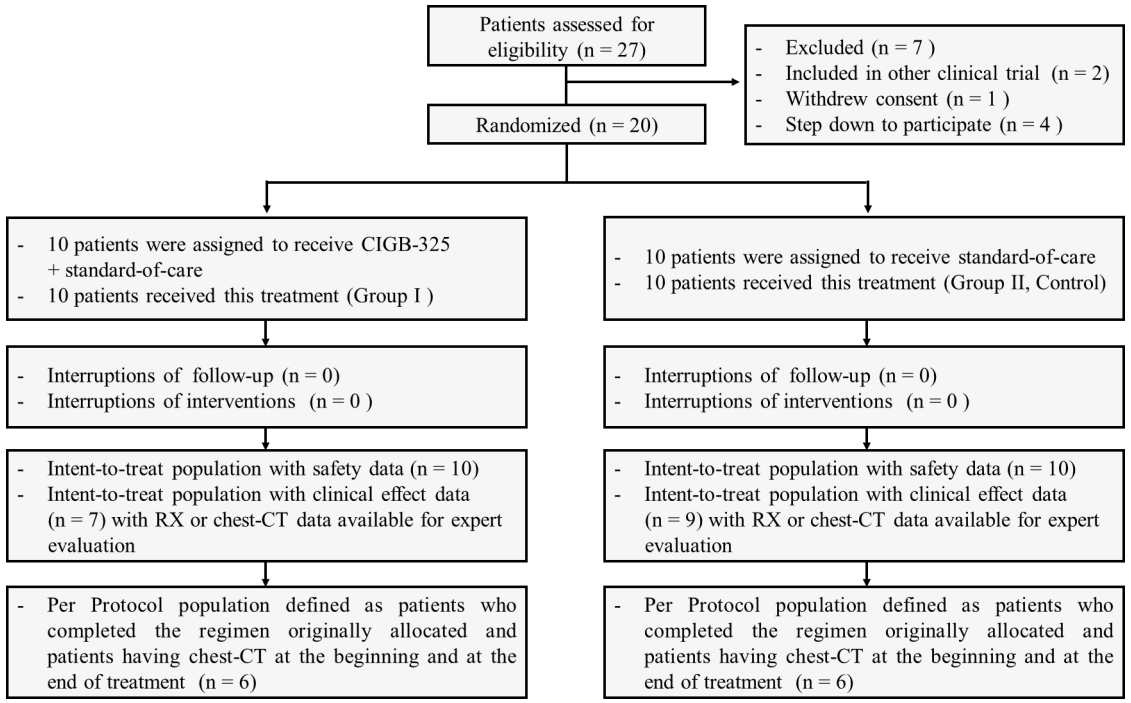

Figure 1. Randomization and enrollment.

placebo-controlled trial of intravenous RDV in adults hospitalized with COVID-19 and lower respiratory tract involvement had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $p < 0.001$).[15]

At present, the main antiviral strategies currently employed against SARS-CoV-2 can broadly be divided into two types: strategies directly targeting the virus and strategies indirectly targeting the virus via host modulation.[16] In both strategies there are already-approved drugs and experimental candidates in clinical trials.[16] Likewise, discovery of novel cellular targets for the SARS-CoV-2 coronavirus has led to novel putative clinical strategies which merit going into clinical research in COVID-19.

Casein kinase 2 (CK2) is a constitutively active Ser/Thr protein kinase deregulated in cancer and other pathologies, responsible for about 20% of the human phosphoproteome.[17] In infectious diseases, CK2 phosphorylates and modulates the function of viral proteins from hepatitis C virus (HCV), vesicular stomatitis virus (VCV), human immunodeficiency virus (HIV), human papilloma virus (HPV), and herpes simplex-1 (HSV-1).[18] Therefore, it is expected that pharmacological intervention with CK2 may impact on any step of the viral life cycle. Recently, CK2 has been found to be directly targeted by the SARS-CoV-2 nucleocapsid protein, and they both colocalize at the filopodia protrusions that promote virus egress and rapid cell-to-cell spread across epithelial monolayers of infected cells.[19] Additionally, inhibition of CK2 in those experiments suggested an instrumental role of this protein kinase for SARS-CoV-2 infection *in vitro*.[19]

Considering the scientific rationality of inhibiting CK2 in SARS-CoV-2 infection, along with the anti-CK2 activity of CIGB-325 (formerly CIGB-300)[20,21] and tolerability of intravenous delivery in human beings,[22,23] we investigated the putative clinical benefit of this peptide-based drug in COVID-19 patients.

On the basis of the FDA recommendations for COVID-19 developing drugs, we performed a small and controlled clinical study.[24] In this exploratory study of proof-of-concept, we administered intravenous CIGB-325 at 2.5 mg/kg along with Cuban standard-of-care for treating SARS-CoV-2 positive patients based on alpha 2b-IFN plus kaletra/hydroxyquinoline. Preliminary data indicated that a combination of CIGB-325 and standard-of-care improved chest-CT outcomes in COVID-19 patients with pneumonia at day 7. Other signs of clinical benefit for this therapeutic regimen were also registered in our study. This is the first clinical study for which an anti-CK2 approach is explored in COVID-19 disease and the preliminary data provided here could warrant larger studies.

RESULTS AND DISCUSSION

Protein kinase CK2 has been recently suggested as a relevant target to combat SARS-CoV-2 infection because of its role on the viral particles egress once accumulated at filopodial protrusions possessing budding viral particles.[19] Although anti-SARS-CoV-2 activity has been demonstrated through *in vitro* models by inhibiting protein kinase CK2, evidence of the clinical benefit of COVID-19 for anti-CK2 approaches is not available at this time. This clinical trial investigated the short-term outcomes of intravenous CIGB-325 at 2.5 mg/kg in a consecutive-5 day regimen which was added to standard care used in COVID-19 disease in Cuba.

Between June 1, 2020, and June 16, 2020, 20 SARS-CoV-2 positive patients underwent randomization in the hospital "Luis Diaz Soto" in Havana, Cuba. A flowchart of the study procedure is presented in Figure 1. Ten were assigned to receive intravenous CIGB-325 + standard-of-care (Group I) and 10 to receive standard-of-care as control (Group II). To diminish odds of severity, the Cuban National Program for managing COVID-19 patients applies standard-of-care just upon confirmation of nasopharyngeal SARS-CoV-2 diagnosis irrespective of symptoms being present or not. The median number of days

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between SARS-CoV-2 diagnosis, hospitalization, and treatment initiation was 2 days. All the patients completed the treatment as planned except one patient from Group I who experienced some concomitant moderate histaminergic adverse events during the first CIGB-325 intravenous delivery, and the dose was decreased to 1.6 mg/kg for the remaining days as indicated in the clinical protocol.

Demographic characterizations among both groups were similar except for age, which was significantly different among both groups (Table 1). Fourteen patients (70%) were asymptomatic at the enrollment and 9 (45%) at the starting day of treatment. Overall, 25% of patients had hypertension, 25% had obesity, and none had type 2 diabetes.

Table 1. Demographic and Clinical Characteristics at Baseline

characteristic	all (N = 20)	CIGB-325 + standard care (N = 10)	standard care (N = 10)
age (years)	45.35 ± 12.0	51.6 ± 11.4	39.1 ± 12.6
Sex no. (%)			
male	14 (70)	8 (80)	6 (60)
female	6 (30)	2 (20)	4 (40)
Skin Color no. (%)			
white	12 (60)	5 (50)	7 (70)
mestizo	2 (20)	1 (10)	1 (10)
black	6 (20)	4 (40)	2 (20)
Coexisting Conditions no. (%)			
hypertension	5 (25)	5 (50)	0 (0.0)
obesity	5 (25)	2 (20)	3 (30)
type 2 diabetes	0 (0.0)	0 (0.0)	0 (0.0)
cancer	1 (5)	1 (10)	0 (0.0)
iron deficiency anemia	1 (5)	0 (0.0)	1 (10)
hypothyroidism	1 (5)	0 (0.0)	1 (10)
glaucoma	1 (5)	0 (0.0)	1 (10)
Clinical Status at Enrollment			
asymptomatic	14 (70)	6 (60)	8 (80)
symptomatic	6 (20)	4 (40)	2 (20)
Clinical Status at the Starting Day of Treatment			
asymptomatic	9 (45)	3 (30)	6 (60)
mild	0 (0.0)	0 (0.0)	0 (0.0)
moderate	9 (45)	5 (50)	4 (40)
severe	2 (10)	2 (20)	0 (0.0)
Symptoms			
headache	3 (15)	2 (20)	1 (10)
anosmia	1 (5)	0 (0.0)	1 (10)
loss of taste	1 (5)	0 (0.0)	1 (10)
fever	2 (10)	2 (20)	0 (0.0)
dry cough	2 (10)	1 (10)	1 (10)
loss of appetite	1 (5)	1 (10)	0 (0.0)
shortness of breath	1 (5)	0 (0.0)	1 (10)
diarrhea	1 (5)	1 (10)	0 (0.0)

In this exploratory study with a small sample size, randomization allowed a balance between the groups regarding the allocation of treatments but not regarding the prognostic variables. Although the sample size in our study is too small to permit generalizability, our data provide a window into what a larger trial might look like.

Data from baseline chest-CT analysis showed that 80% of patients in the CIGB-325 group had positive chest-CT according to the presence of ground-glass opacity, consolidation, mix pattern, and affectation of more than three pulmonary lobules. The mix pattern was the most predominant lesion. In the control group, 50% of patients had positive chest-CT with the presence of consolidation, mixed pattern, and affectation of less than two pulmonary lobules.

Concerning hematological and biochemical baseline parameters in all patients, abnormal levels were observed in hemoglobin (25%), platelets (15%), neutrophils (50%), lymphocytes (40%), aspartate aminotransferase (ASAT) (20%), alanine aminotransferase (ALAT) (40%), ferritin (35%), creatinine (20%), and glycemia (30%). Other parameters were in the normal range.

Data from safety analysis indicated that intravenous CIGB-325 added to standard-of-care did increase both frequency of adverse events and patients with adverse events (Table 2). Particularly, pruritus, flushing, and rash were increased by CIGB-325 treatment in 100, 80, and 60% of patients, respectively. As previously observed during CIGB-325 intravenous administration, intensity of this kind of adverse events was mild and/or moderate in all of the patients.

The safety profile of CIGB-325 plus standard-of-care was very similar to that observed for CIGB-325 alone in which a predominant pattern of transient histaminergic-like side effects was observed.[22] However, the intensity of the side effects was mild and/or moderate in all the patients and total resolution of them was achieved at no more than 1 h after CIGB-325 administration. Thus, our study revealed that a combination of intravenous CIGB-325 at 2.5 mg/kg with standard care for COVID-19 is a manageable and safe strategy to treat patients with this infectious disease.

The dynamic conversion from positive to negative of the SARS-CoV-2 real-time transcriptase polymerase chain reaction (RT-PCR) results was also analyzed in both groups of treatments at 0, 3, 7, and 14 days. No significant differences were observed in the median time, 11 days ± 8.0 for CIGB-325 plus standard care and 12 days ± 6 for standard care alone (p = 0.614). Thus, time to SARS-CoV-2 viral clearance in the nasopharynx swabs behaved similarly for both treatments over time. Therefore, other regimens with different frequency and/or CIGB-325 dose levels merit exploration to follow viral clearance in future trials. Nonetheless, the usefulness and feasibility of the viral end point in nasopharyngeal swabs to assess anti-SARS-CoV-2 drugs has not been established yet. Instead, clinical end points seem to be more informative in the COVID-19 disease.[11,15,24]

The clinical status was classified in categories of asymptomatic, mild, moderate, or severe disease, and it was followed up until ending treatment and thereafter for both groups. In the intent-to-treat population of the CIGB-325 group at day 6 there were 2/10 patients that remained asymptomatic since initiation of treatment, 2/10 changed from severe to moderate, 1/10 from moderate to asymptomatic, 1/10 from mild to asymptomatic, and 4/10 did not change their clinical status during the treatment. Otherwise, in the control 6/10 patients remained asymptomatic since initiation of treatment, 1/10 changed from mild to asymptomatic, and 3/10 did not change their clinical status during the treatment. Thus, improvement of the clinical status at day 7 trended to be superior by adding CIGB-325 to the standard-of-care.

Additionally, chest-CT analysis was performed to investigate the effect of CIGB-325 over the COVID-19 pulmonary lesions. For that purpose, both number and lesion's extent at day 0 and after treatment (day 7) were compared just in those patients

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Table 2. Adverse Events

	Group I[a]				Group II[a]			
	patients		events		patients		events	
	frequency	%	frequency	%	frequency	%	frequency	%
N	10	100	109	100	10	100	7	100
pruritus	10	100.0	48	44.0				
rash	6	60.0	12	11.0				
flush	8	80.0	23	21.1				
hot flashes	5	50.0	12	11.0				
wheals	3	30.0	5	4.6				
bradycardia	1	10.0	1	0.9				
cramps	2	20.0	2	1.8	1	10.0	1	14.3
trembling	2	20.0	2	1.8				
chills	1	10.0	1	0.9				
nausea	1	10.0	1	0.9	1	10.0	2	28.6
tinnitus	1	10.0	2	1.8				
diarrhea					1	10.0	2	28.6
headache					1	10.0	2	28.6

[a]Group I: CIGB-325 plus standard-of-care; Group II: standard-of-care

Table 3. Chest-CT Evolution Considering Number of Pulmonary Lesions

			Group I $N^a = 6$	Group II $N^a = 7$	Sign. (U-Mann−Whitney)
no of lesions	Day 0	median ± RI (min; max)	9.5 ± 10.0 (0; 18)	3.0 ± 5.0 (0; 10)	0.051
	Day 7	median ± RI (min; max)	5.5 ± 10.0 (0; 17)	2.0 ± 5.0 (0; 6)	0.149
		Sign. (Wilcoxon)	0.042	0.680	
reduction of lesions		yes	5 (83.3%)	3 (42.9%)	0.266 (Fisher)
		no	1 (16.7%)	4 (57.1%)	
		Dif. (IC 95%)	41.4 (−6.9; 78.6)		Bayesian analysis
		P (Dif. > 0)	0.951		

[a]Per protocol population defined as patients who completed the regimen originally allocated and patients having chest-CT at the beginning and at the end of treatment.

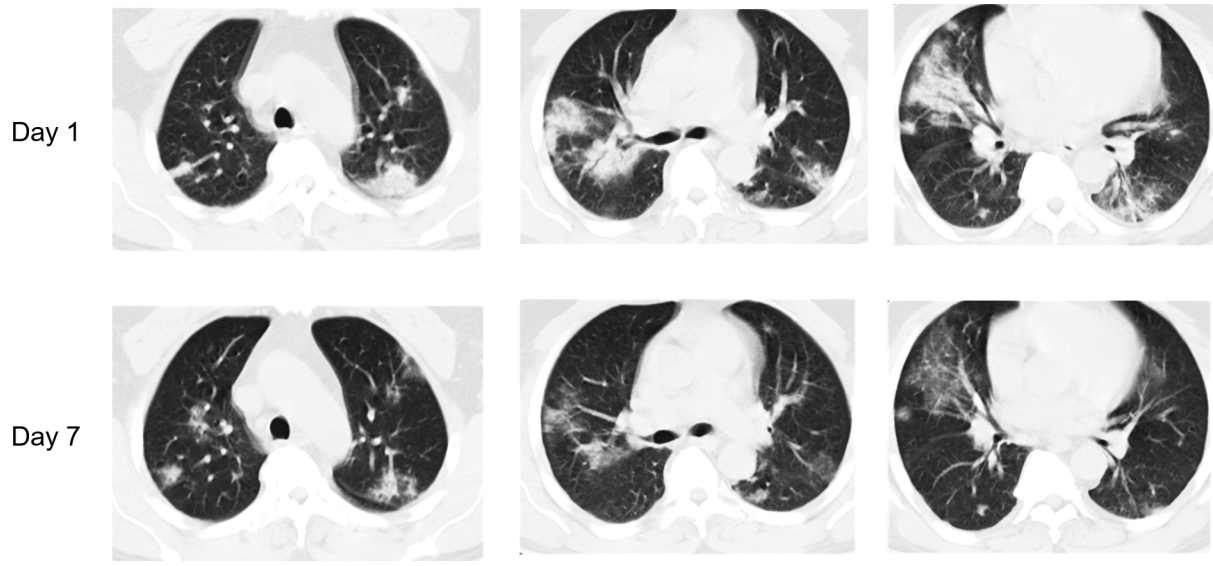

Figure 2. Representative chest-CT images from one patient in the CIGB-325 group at day 0 and 7.

analyzed per protocol (Table 3). Importantly, CIGB-325 treatment significantly reduced the median number of pulmonary lesions from 9.5 ± 10 (day 0) to 5.5 ± 10 (day 7) ($p = 0.042$). Conversely, no substantial change was observed in the control group. The proportion of patients with reduction of pulmonary lesions was higher in the CIGB-325 group compared with the control according to the Bayesian analysis (pDif > 0; 0.951) (Table 3).

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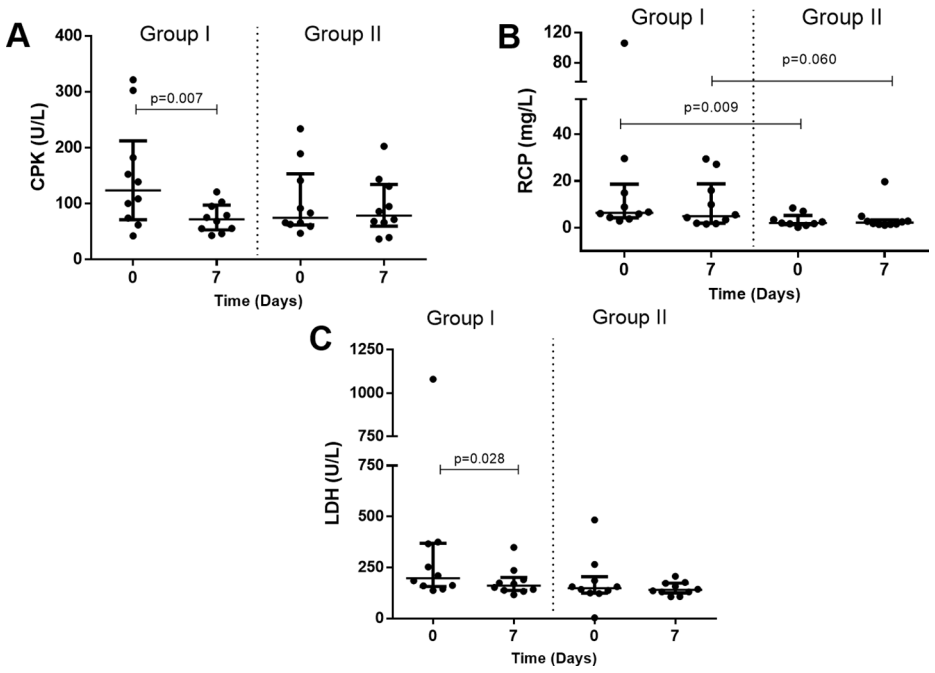

Figure 3. Serum levels of COVID-19 linked markers. Serum levels of CPK (A), RCP (B), and LDH (C). Group I: CIGB-325 + standard-of-care. Group II: standard-of-care.

The effect of the lesion's extent shown in Table S1 indicates that CIGB-325 treatment also reduced the median of the lesion's extent after a consecutive-5 day regimen although not significantly. Otherwise, any kind of reduction was observed in the control group. Importantly, the proportion of patients with the reduction of the lesion's extent was higher in the CIGB-325 group (4/7) compared with control (1/9) (pDif > 0; 0.982) (Bayesian analysis). Representative images of the chest-CT evolution from one CIGB-325 treated patient are shown in Figure 2.

These preliminary results suggest a quick clinical benefit with CIGB-325 treatment particularly evidenced by the chest-CT data at day 7 post-treatment initiation. Specifically, CIGB-325 treatment fostered reduction of both the number of pulmonary lesions and lesion's extent at day 7, and also the proportion of patients exhibiting this inhibitory effect is superior in the CIGB-325 group compared with that of the standard-of-care group. The chest-CT response observed in our trial could be explained by direct antiviral activity of CIGB-325 in SARS-CoV-2 infected pneumocytes.[25] Accordingly, unpublished *in vitro* data from our laboratory have documented anti-SARS-CoV-2 effect of CIGB-325 in Vero-E6 cells.

The improvement of chest-CT response by the addition of CIGB-325 to standard-of-care could have a great clinical impact in avoiding progression to severity of COVID-19 patients. Additionally, our study shows that alpha 2b IFN + kaletra/hydroxychloroquine also reduces pulmonary lesions at day 7 although to a lesser extent. Such an effect rather might be by the previously reported anti-SARS-CoV-2 activity of type I IFNs when administered either by the parenteral route or inhaled.[26]

Several laboratory parameters may facilitate the assessment of disease severity and rational triaging.[27] In this work we also investigated the levels of creatinine phospho kinase (CPK), reactive C-protein (RCP), and lactate dehydrogenase (LDH) in plasma. Of note, data from Figure 3 show that CIGB-325 treatment significantly reduced the CPK ($p = 0.007$) and LDH ($p = 0.028$) serum levels. Also, the RCP values were lowered by CIGB-325 treatment although with no statistical difference. Importantly, high serum CPK levels have been associated to rhabdomyolysis, weakness, and heart injury in COVID-19 patients; therefore, these findings also support the clinical benefit of using CIGB-325 in this viral disease. Likewise, reduction of inflammatory markers such as LDH and CRP by CIGB-325 could support a putative anti-inflammatory effect of this clinical strategy in COVID-19.

Finally, our study gave interesting clues suggesting a quick clinical benefit at day 7 by using an anti-CK2 approach which has not been reported so far for COVID-19. Whether CIGB-325 prevents COVID-19 from getting worse by inducing an antiviral effect in the lungs and preventing damage caused by the virus is something that merits further investigation in larger clinical trials.

METHODS

Patients. From June 1 to June 16, 2020, 20 patients confirmed as SARS-CoV-2 positive by RT-PCR were enrolled in a monocentric parallel group design in therapeutic exploratory trial at the "Luis Diaz Soto" Hospital in Havana, Cuba (https://rpcec.sld.cu/trials/RPCEC00000317-En, Code: IG/CIGB300I/CV/2001, ATENEA-Co-300 trial). CIGB-300 code used for cancer treatment was substituted by CIGB-325 just after the online registration of this clinical trial; therefore, it appears with the former code. The Ethics Committee for Clinical Research in the hospital and Cuban Regulatory Agency (CECMED) approved the trial. The study complied with the Good Clinical Practices and the precepts established in the Declaration of the Helsinki World Medical Association. All patients met the inclusion criteria described in the protocol and signed the informed consent.

Laboratory Examination. Laboratory results included blood routine, leucocyte subsets, and blood biochemical parameters. Serum levels of CPK, LDH, and RCP were determined by a specific Roche system (Roche-cobas-C311).

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SARS-CoV-2 Viral Dynamic in Nasopharyngeal Swabs. Nasopharyngeal swabs were obtained from patients at days 0, 3, 7, and 14. Viral RNA was detected by RT-PCR amplification by using specific SARS-CoV-2 primers. The presence of SARS-CoV-2 in swabs was followed-up at indicated times and compared among both groups.

Clinical Response. Clinical status was classified as asymptomatic, mild, moderate, or severe COVID-19 disease according to the NIH guide "Coronavirus Disease 2019 (COVID-19) Treatment guidelines". https://www.covid19treatmentguidelines.nih.gov. The chest-CT analysis was performed considering the number of pulmonary lesions, the lesion's extent, and common COVID-19 typical abnormalities such as consolidation, glass-round opacity, and mix pattern.

Safety. Pretreatment evaluation included a detailed history and physical examination. In addition, hematological counts, blood chemistry, coagulation, radiography, and chest-CT studies were performed. Systemic toxicity was evaluated daily after each CIGB-325 administration. Severity of adverse events was classified by the WHO Adverse Reaction Terminology. Causal relationship was classified as very probable (definitive), probable, possible, or remote (doubtful).

Statistical Analysis. For chest-CT variables, the analysis was performed in per protocol population defined as patients who completed the regimen originally allocated and patients having chest-CT at the beginning and at the end of treatment. Continuous variables were expressed as mean and standard deviations or median and interquartile ranges (depending on the assumption of normal distribution). The Student-*t* test or Mann−Whitney U test was applied to continuous variables, and chi-square or Fisher's exact test were used for categorical variables. For the variation in time in each group, the Wilcoxon-rank test or Student-*t* test for dependent variables was used. A type 1 error of 0.05 was specified. Considering the small sample size, the differences between groups (for clinical and chest-CT evaluations, proportion of patients with reduction of score, and number of lesions) were estimated from the Bayesian point of view, performing 10 000 simulations and specifying non-informative prior distributions. The analysis was performed using SPSS 25.0 software and EPIDAT 3.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsptsci.0c00175.

Chest-CT evolution considering lesion's extent (PDF)

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Notes

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■ REFERENCES

(1) https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200809-COVID-19-sitrep-202 (accessed September 15, 2020).

(2) https://coronavirus.jhu.edu/map.html (accessed September 15, 2020).

(3) Cohen, P. A., Hall, L., John, J. N., and Rapoport, A. B. In *The early natural history of SARS-CoV-2 infection: Clinical observations from an urban, ambulatory COVID-19 clinic*, Mayo Clinic Proceedings, 2020, Elsevier, 2020; pp 1124−1126.

(4) Wu, Z., and McGoogan, J. (2020) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA 323*, 10.

(5) Wu, J., Mafham, M., Mamas, M., Rashid, M., Kontopantelis, E., Deanfield, J., de Belder, M., and Gale, C. P. (2020) Place and underlying cause of death during the COVID19 pandemic: retrospective cohort study of 3.5 million deaths in England and Wales, 2014 to 2020. *medRxiv*, DOI: 10.1101/2020.08.12.20173302.

(6) Phillips, R. O., Robert, J., Abass, K. M., Thompson, W., Sarfo, F. S., Wilson, T., Sarpong, G., Gateau, T., Chauty, A., and Omollo, R. (2020) Rifampicin and clarithromycin (extended release) versus rifampicin and streptomycin for limited Buruli ulcer lesions: a randomised, open-label, non-inferiority phase 3 trial. *Lancet*, 1259.

(7) Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris, A., Sanseau, P., Cavalla, D., and Pirmohamed, M. (2019) Drug repurposing: progress, challenges and recommendations. *Nat. Rev. Drug Discovery 18* (1), 41−58.

(8) Ohashi, H., Watashi, K., Saso, W., Shionoya, K., Iwanami, S., Hirokawa, T., Shirai, T., Kanaya, S., Ito, Y., and Kim, K. S. Multidrug treatment with nelfinavir and cepharanthine against COVID-19. *bioRxiv* 2020, DOI: 10.1101/2020.04.14.039925.

(9) Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J., Lv, Q., Liu, J., Yu, P., and Xu, Y. Lack of reinfection in rhesus macaques infected with SARS-CoV-2. *bioRxiv* 2020, DOI: 10.1101/2020.03.13.990226.

(10) Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., and Wei, M. (2020) A trial of lopinavir−ritonavir in adults hospitalized with severe COVID-19. *N. Engl. J. Med. 382*, 1787.

(11) Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., et al. (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet 395*, 1569.

(12) Borba, M. G. S., Val, F. F. A., Sampaio, V. S., Alexandre, M. A. A., Melo, G. C., Brito, M., Mourão, M. P. G., Brito-Sousa, J. D., Baía-da-Silva, D., and Guerra, M. V. F. (2020) Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Network Open 3* (4), e208857−e208857.

(13) Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., and Yang, Y. (2020) Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering 6*, 1192.

(14) Bauchner, H., and Fontanarosa, P. B. (2020) Randomized clinical trials and COVID-19: managing expectations. *J. Am. Med. Assoc. 323*, 2262.

(15) Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., et al. (2020) Remdesivir for the treatment of COVID-19—preliminary report. *N. Engl. J. Med. 383*, 1813.

(16) Ahidjo, B. A., Loe, M., Ng, Y. L., Mok, C. K., and Chu, J. J. H. (2020) Current Perspective of Antiviral Strategies against COVID-19. *ACS Infect. Dis. 6*, 1624.

(17) Meggio, F., and Pinna, L. A. (2003) One-thousand-and-one substrates of protein kinase CK2? *FASEB J. 17* (3), 349−68.

(18) Keating, J. A., and Striker, R. (2012) Phosphorylation events during viral infections provide potential therapeutic targets. *Rev. Med. Virol. 22* (3), 166−81.

(19) Bouhaddou, M., Memon, D., Meyer, B., White, K. M., Rezelj, V. V., Marrero, M. C., Polacco, B. J., Melnyk, J. E., Ulferts, S., Kaake, R. M., et al. (2020) The global phosphorylation landscape of SARS-CoV-2 infection. *Cell 182* (3), 685−712. e19.

(20) Perea, S. E., Reyes, O., Puchades, Y., Mendoza, O., Vispo, N. S., Torrens, I., Santos, A., Silva, R., Acevedo, B., López, E., Falcón, V., and Alonso, D. F. (2004) Antitumor effect of a novel proapoptotic peptide that impairs the phosphorylation by the protein kinase 2 (casein kinase 2). *Cancer Res. 64* (19), 7127−9.

(21) Perera, Y., Ramos, Y., Padron, G., Caballero, E., Guirola, O., Caligiuri, L. G., Lorenzo, N., Gottardo, F., Farina, H. G., Filhol, O., Cochet, C., and Perea, S. E. (2020) CIGB-300 anti-cancer peptide regulates the protein kinase CK2-dependent phosphoproteome. *Mol. Cell. Biochem. 470*, 63.

(22) García-Diegues, R., and de la Torre-Santos, A. (2018) Phase I Study of CIGB-300 Administered Intravenously in Patients with Relapsed/Refractory Solid Tumors. *ARCHIVOS DE MEDICINA 1* (1), 4.

(23) Fernández Águila, J. D., García Vega, Y., Ríos Jiménez, R. O., López Sacerio, A., Rodríguez Rodríguez, C. R., Rodríguez Fraga, Y., and Valenzuela Silva, C. (2016) Safety of intravenous application of cigb-300 in patients with hematological malignancies. EHPMA study. *Revista Cubana de Hematología, Inmunología y Hemoterapia 32* (2), 236−248.

(24) https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs (accessed September 15, 2020).

(25) Carsana, L., Sonzogni, A., Nasr, A., Rossi, R. S., Pellegrinelli, A., Zerbi, P., Rech, R., Colombo, R., Antinori, S., Corbellino, M., Galli, M., Catena, E., Tosoni, A., Gianatti, A., and Nebuloni, M. (2020) Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect. Dis. 20*, 1135.

(26) Pereda, R., Gonzalez, D., Rivero, H. B., Rivero, J. C., del Rosario Lopez, L., Mezquia, N., Venegas, R., Betancourt, J. R., and Dominguez, R. E. (2020) Therapeutic effectiveness of interferon alpha 2b treatment for COVID-19 patient recovery. *medRxiv*, DOI: 10.1101/2020.07.28.20157974.

(27) Velavan, T. P., and Meyer, C. G. (2020) Mild versus severe COVID-19: Laboratory markers. *Int. J. Infect. Dis. 95*, 304−307.