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ORIGINAL ARTICLE

Safety, anti-inflammatory and antiviral effect of anti- SARS-CoV-2 Gamma globulin in severe COVID-19 patients

Seguridad y exploración del efecto antiinflamatorio y antiviral de la Gammaglobulina anti SARS-CoV-2 en pacientes graves con la COVID-19

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ABSTRACT

Introduction: Antiviral therapy is a treatment for COVID-19. During the pandemic, hyperimmune immunoglobulin was produced as a treatment for infected patients.

Objective: To evaluate the safety and explore the anti-inflammatory and antiviral effect of anti-SARS-CoV-2 gamma globulin in severely ill patients with COVID-19.

Material and Methods: An exploratory, open-label, monocenter and controlled clinical trial was performed. Two groups of patients with diagnosis confirmed by real-time polymerase chain reaction were randomized; they consisted of a control group of 10 patients and a group of 11 patients who were administered hyperimmune immunoglobulin in a single dose (150 mg/kg). Both groups received treatment according to the national protocol for COVID-19 patients and were evaluated for 7 days.

Results: No causally related serious adverse events were reported; the probability of an attributable serious adverse event was 8%. In the intervention group, both mean neutrophil/lymphocyte ratio and C-reactive protein values decreased. Real time-lapse polymerase chain reaction (RT-PCR) increased slightly, and D-dimer levels remained unchanged. Favorable outcomes were seen on X-ray in 10/11 patients (95% CI [58.7; 98.7]), and on CT in 5/11 patients (95% CI [16.7; 76.6]). In the treated group, 72.7% of patients improved in severity parameters and 2/11 worsened (95% CI [2.3; 51.8]); none required mechanical ventilation. The median time in the Intensive Care Unit was 7.5 days, and the median time of hospital stay was 11 days.

Conclusions: Anti-SARS-CoV-2 gamma globulin showed evidence of safety and favorable outcome at the 7th day of treatment.

Keywords:
Clinical trial, pandemic, SARS-CoV-2, gamma globulin, anti-SARS-CoV-2, antiviral therapy.

RESUMEN

Introducción: La terapia antiviral es un tratamiento para la COVID-19. Durante la pandemia se produjo una inmunoglobulina hiperinmune, como tratamiento de los pacientes infectados.

Objetivo: Evaluar la seguridad y explorar el efecto antiinflamatorio y antiviral de la gammaglobulina anti-Sars-CoV-2 en pacientes graves con la COVID-19.

Material y Métodos: Ensayo clínico exploratorio, abierto, monocéntrico, con control. Se aleatorizaron 2 grupos de pacientes, con diagnóstico confirmado por reacción en cadena de la polimerasa en tiempo real. Un grupo control de 10 pacientes y un grupo de 11 pacientes al que se le administró la inmunoglobulina hiperinmune en dosis única (150 mg/kg), ambos grupos recibieron tratamiento del protocolo nacional para pacientes COVID-19 y fueron evaluados por 7 días. La variable principal fue frecuencia de eventos adversos graves en relación causal, cota máxima de 10 %.

Resultados: No se reportó ningún evento adverso grave con relación causal, la probabilidad de evento adverso grave atribuible fue de 8 %. En el grupo de la intervención disminuyeron ambos valores medios del índice neutrófilos/linfocitos y de proteína C reactiva. El ciclo de amplificación de la reacción en cadena de la polimerasa en tiempo real aumentó ligeramente y el dímero D no tuvo variaciones. Fue favorable la evolución en radiografía en 10/11 pacientes, IC 95 % (58,7; 98,7) y por tomografía en 5/11, IC 95 % (16,7; 76,6). En el grupo tratado 72,7 % de los pacientes mejoraron parámetros de gravedad y empeoraron 2/11, IC 95 % (2,3; 51,8), ninguno necesitó ventilación mecánica. La mediana del tiempo en Unidad de Cuidados Intensivos fue 7,5 días y de hospitalización 11 días.

Conclusiones: La Gammaglobulina anti-Sars-CoV-2 mostró evidencias de seguridad y evolución favorable al 7mo día.

Palabras Claves:
Ensayo clínico, pandemia, SARS-CoV-2, Gammaglobulina, anti-Sars-CoV-2, terapia antiviral.

INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Immunity to infection is flawed in the interferon system in early stages with an increase in pro-inflammatory interleukins.[1,2] Humoral immune response produces neutralizing antibodies that prevent viral dissemination. The weak action of antibodies is associated with an unfavorable evolution of the disease.[3] The plasma obtained from convalescent patients has heterogeneous antibodies. Some research works allowed to develop clinical trials to use serum taken from convalescent COVID-19 patients in the treatment of severely ill patients, where favorable results were evidenced.[4,5]

Plasma derivatives from convalescent COVID-19 patients are IgG formulations with neutralizing action that exceeds a plasma bag in purity.[4,6] They are derived from healthy individuals that recovered from COVID-19 and developed a robust humoral immune response.[6] During the COVID-19 pandemic, their use was expanded in different clinical settings in order to evaluate the effect on severe forms of the disease.[7]

In Cuba, based on the evidence of international studies, AICA laboratories developed the first product with specific antiviral activity against SARS-CoV-2, derived from a plasma pool obtained from individuals with specific antibodies who had recovered from the disease. The anti-SARS-CoV-2 hyperimmune immunoglobulin has a concentration of proteins of 5g/100 mL (5%) and an activity of 300 IU/mL. This IgG is capable of neutralizing the virus, thus modifying the immune response in such a way that seriously ill patients can have a more favorable evolution and avoid a critical stage and the death.[8]

This article reports the first study carried out on the product; its main **objective** is to evaluate the safety and explore the anti-inflammatory and antiviral effect of anti-SARS-CoV-2 gamma globulin in severe COVID-19 patients.

MATERIALS AND METHODS

An exploratory, open, randomized with concurrent reference control, and homocentric clinical trial was designed at the initial stage of the product development strategy. The study was performed at "Dr. Luis Díaz Soto" Hospital in the period between July 21st and September 14th, 2021.

The study protocol was approved by the Center for State Control of Medicines and Medical Devices (CECMED), and by the Research Ethics Committee (REC). All patients gave their written informed consent for participation. The trial was registered in the Cuban Public Registry of Clinical Trials with the code: RPCEC 00000379 (https://rpcec.sld.cu/ensayos/RPCEC00000379-Sp).

A total of 21 patients with diagnosis confirmed by real time-lapse polymerase chain reaction (RT-PCR), infected by SARS-CoV-2, hospitalized, and seriously ill, were included in the study. They were considered seriously ill if they had at least one of the following criteria: pneumonia, presence of signs of alarm or increasing dyspnea, respiratory rate (RR) > 25 inspirations/min, blood oxygen saturation (SpO2) < 93%, oxygen therapy to maintain SO2 > 93%, a PaO2/ FiO2 ratio < 250 mm Hg, and a radiograph (Rx) showing an inflammatory infiltration of more than 50% in both lung fields.

The patient selection criteria included:

Inclusion criteria: patients over 19 years of age, with less than 10 days of onset of symptoms, and informed consent for participation.

Exclusion criteria: ventilated patients; with chronic kidney disease; with history of thromboembolic events, anaphylaxis or adverse reaction to intravenous gamma globulin; pregnant or breastfeeding; having severe comorbidities (terminal cancer, severe heart disease); with Body Mass Index ≥ 30; with selective IgA deficiency; presenting autoimmune diseases; following treatment with anti-CD6 monoclonal antibody Itolizumab; and using hemoderivatives for less than one month.

The patients were selected (1:1) from an automated random list, using the balanced block allocation method. The implementation was performed using sealed envelopes at the clinical site.

The control group received treatment according to the national action protocol for COVID-19 patients, version 1.6 (except Itolizumab). The intervention group received the same treatment, besides anti-SARS-CoV-2 gamma globulin at a dose of 150 mg/kg of body weight (1100 IU/Kg), in single dose, diluted in 500 mL of 0.9% saline solution, administered intravenously for a period of no less than two hours. The dose decision was made taking into account the doses used in international essays (described in the discussion), as well as the low availability of plasma. Before infusion, (30 min) Hydrocortisone 100 mg or any other equivalent short-acting glucocorticoid was administered intravenously, as well as a Diphenhydramine dose of 25 mg.

The principal safety variable was the occurrence of serious adverse events (SAEs) with a causal relationship (probable, possible, definite) with the product, according to the adverse event reporting classification of the CECMED. A safety hypothesis was established with a minimum threshold of 10%. The safety profile was recorded by type of adverse events, as well as characteristics, duration, intensity, causality, course of action, and outcome. The vital signs studied included: temperature, systolic blood pressure, diastolic blood pressure, pulse, and respiratory rate.

The exploratory variable of antiviral response was the real time-lapse polymerase chain reaction (RT-PCR) though the amplification cycle (Ct). It was classified as reactive or non-reactive, and Ct values were described at each time point. The absolute change from the initial value to the final value was determined. The increase in value with respect to the initial value corresponds to the response. The anti-inflammatory response variable consists of: neutrophil-to-lymphocyte ratio (NLR). Values were recorded on days 0, 3, 5, and 7, along with the absolute change from the initial value to the final value, C-reactive protein and D-dimer. The values and the absolute change from the initial value to the final value were described on days 0, 3, 5, and 7. It was recorded whether there was a decrease in the values on day 7 with respect to the initial value. In addition, a summary variable indicating a favorable response was described if there was not an increase in the Ct and a decrease in the three parameters of anti-inflammatory response.

The secondary variables used to assess clinical evolution were: worsening of clinical status, which was defined as the occurrence of at least one of the following events: need for mechanical ventilation, increased respiratory rate, decreased oxygen saturation, worsening of X-ray images, shock, disseminated intravascular coagulation, multiple organ failure, and death. To evaluate the improvement of the severity criterium, it was recorded daily whether or not the patient presented each of the following severity parameters: (SpO2 < 93%, need for oxygen therapy to maintain SpO2 > 93%, PaO2/FiO2 ratio < 250 mm Hg, respiratory rate ≥ 25 breaths/min, infiltrates in more than 50% of both lung fields). The evolution of the improvement at each moment with respect to the initial moment was evaluated.

Evaluation using computed tomography (CT) and X-ray imaging was carried out according to the definitions of the National Imaging Group, established by the Cuba´s Consensus Proposal for standardized and structured reporting models for COVID-19 patients. X-ray evaluation was performed using a scoring system based on the modified X-ray scoring system in evaluating severity of COVID-19 patients.[9] Patients´ evolution at 7 days was defined as: favorable, stationary, or unfavorable; the first one was determined when the score decreased and there were no qualitative complications; it was considered stationary if it remained the same in both variables, and unfavorable if the score increased and/or there were qualitative complications. CT evaluation was based on the type and extent of lesions. Patient´s evolution was defined as favorable if the extent improved or regressed, stationary if it remained the same, and unfavorable if there was a worsening of the extent and/or type of lesion.

The initial exploratory study carried out as part of the development of the intervention defined a sample size of 15 in the intervention group, which was calculated using the binomial distribution, specifically designed for pilot studies, considering a 10% upper toxicity limit and an 80% confidence level as well as a reference concurrent control with similar size. Because of the small sample size and the low frequency expected on related serious adverse events (SAEs), a Bayesian strategy was planned for evaluating the primary variable and making decisions. A *priori* distribution was considered uninformative due to the lack of previous information; from the observed data, the 95% probability interval (maximum likelihood interval), probability of AEs related to the product, and toxicity probability lower than 10% were estimated.

All assigned patients were included in the analysis; all the missing data were imputed using the last observation carried forward (LOCF) method. Estimates were obtained by group for the antiviral (Ct RT-PCR) and anti-inflammatory response variable (INL, C-reactive protein, and D-dimer); descriptive statistics were used for each evaluation moment (day 0, 3, 5, and 7). Values (median and interquartile range) and change from the baseline were described. Evolution was assessed using the Wilcoxon signed-rank test, a non-parametric paired test. Improvement was defined in all cases, according to the response criterion: increased (Ct RT-PCR) or decrease in baseline values (INL, C-reactive protein, and D-dimer). Proportions were estimated, and 95% confidence intervals (exact two-tailed) were calculated for each group. A similar analysis was performed for all secondary variables.

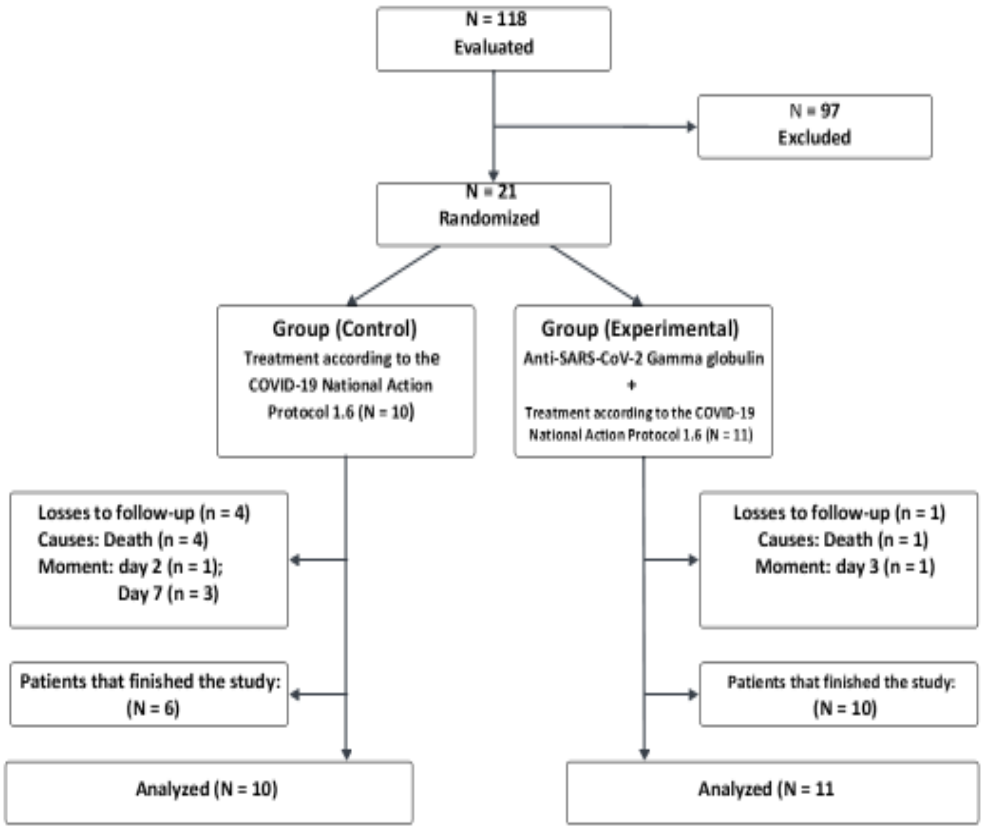
The study was designed and conducted in accordance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, adopted by the World Medical Assembly). The 7th revision at the 64th General Assembly in Fortaleza, Brazil, October 2013, was taken into account.[10] It complied with the ethical standards and criteria established in international[11] and national codes of ethics, as well as the legal regulations of the current Cuban Drug Regulatory Agency.[12]

The conduct and monitoring of the clinical study were carried out in accordance with the Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH)[13] and the Document of the Americas.[11] The Cuba´s current regulations concerning the conduct of clinical trials and the working procedures of the National Clinical Trials Coordinating Center (CENCEC), which follows the ICH Guidelines and Regulation 165-2000 of the Cuban Center for State Control of Medicines and Medical Devices (CECMED), were also taken into account.[14]

RESULTS

A total of 118 hospitalized patients were evaluated and 21 patients were included by selection criteria; 10 patients were placed in the control group, and the remaining 11 were part of the group treated with gamma globulin in a single dose, on the same day of inclusion. Five patients died; therefore, they did not complete the 7-day study, and 4 patients were part of the control group. (Figure 1)

Figure 1. Distribution of patients during the study



The demographic and clinical characteristics of patients are presented in Table 1. In both groups, the age ranged from 44 to 84 years old; two-thirds were male, and the time of onset of symptoms was between 4 and 11 days. In the control group, there was predominance of patients with SpO2< 93%, PaO2/FiO2 ratio < 250 mm Hg, RR> 25, and need of oxygen requirement, which constitute indicative values of disease severity.

Table 1: Clinical and Demographic characteristics

Variables		Control Group	Intervention Group
Age (years)	Mean (SD)	67 (11)	58 (12)
	Median (p25, p75)	71 (60 -72)	55 (47- 66)
	(Min.; Max.)	(48; 84)	(44; 82)
Days since the onset of symptoms	Median (p25, p75)	9 (8 -10)	10 (6 -10)
	Min, Max	(5; 11)	(0; 10)
Sex, n (%)	Female	3 (30.0)	3 (27.3)
	Male	7 (70.0)	8 (72.7)
Skin color, n (%)	White	7 (70.0)	8 (72.7)
	Mixed-race	1 (10.0)	2(18.2)
	Black	2 (20.0)	1 (9.1)
Patient with comorbidity, n (%):	At least one of the following types: DM, AHT; Obesity; COPD	9 (90.0)	8 (72.7)
	Diabetes Mellitus	6 (60.0)	2 (18.2)
	Arterial Hypertension	9 (90.0)	6(54.5)
	Obesity (BMI ≥30)	0 (0.0)	3 (27.3)
Lung disease, n (%)	Type: Bronchial asthma	2 (20.0)	2 (18.2)
Other comorbidities, n (%)	Diabetic Neuropathy	1 (10.0)	1 (9.1)
	Prostatic Hyperplasia	1 (10.0)	1 (9.1)
	Ischemic cardiopathy	2 (20.0)	1 (9.1)
	Senile Dementia	1 (10.0)	0 (0.0)
	Parkinson´s Disease	1 (10.0)	0 (0.0)
	Glaucoma	1 (10.0)	0 (0.0)
	Hipothyroidism	0 (0.0)	1 (9.1)
	Tuberculosis	0 (0.0)	1 (9.1)
Initial RT-PCR, n (%)	Positive	10 (100.0)	11 (100.0)
Admitted to the ICU, n (%)	Yes	9 (90.0)	7 (63.6)
Severity at onset, n (%)	Pneumonia	10 (100.0)	11 (100.0)
	SpO2 < 93%	6 (60.0)	3 (27.3)
	Need of oxygen to maintain SO2 > 93%	8 (80.0)	5 (45.5)
	PaO2/FiO2 ratio < 250 mm Hg	6 (60.0)	2 (18.2)
	Respiratory Rate > 25	4 (40.0)	2 (18.2)
	Respiratory infiltrates on X-ray > 50% in both LF*	4 (40.0)	2 (18.2)
Initial Ct RT PCR values*	Mean (SD)	27.2 (4.0)	24.1 (7.2)
	Median (p25- p75)	28 (26 - 30)	25 (23-29)
	Min, Max	(20.1; 34.1)	(10.2; 33.7)
Classified initial Ct values*, n (%)	< 25	2 (20.0)	5 (45.5)
	> 35	0 (0.0)	0 (0.0)

The characteristics of adverse events and safety assessment during 7 days are shown in Table 2. None of the patients presented serious adverse events (SAE) causally related to Gamma globulin. The probability of occurrence related to SAE was low (0.08), and the possibility that this proportion could be lower than 10% was 0.28. The 95% interval of maximum verosimilarity for the frequency of those events was (0.0; 0.2).

In this study, a total of 13 adverse events (AEs) were reported in 6 patients belonging to the group treated with gamma globulin, while 8 patients presented 22 AEs in the control group. Six adverse events, which included headache, hyperglycemia, fever (reported twice in the same patient), acute respiratory insufficiency (1 patient), and arterial hypertension (1 patient), were reported in 5 patients during the same day of treatment with Gamma globulin. In that group, frequent adverse events such as arterial hypertension (4 times in 3 patients) and fever (twice in the same patient) had an incidence greater than 10%. Acute respiratory failure was the serious adverse event (SAE) that caused a patient´s death. There was no causal relationship between AEs and the intervention. Hypoxemia and acute respiratory failure were reported 3 times (3 patients) in the control group; in this group, there was a predominance of moderate and severe AEs (9 times each). There were 14 AEs, 10 of them caused the death of 4 patients (three due to severe hypoxia, and a pulmonary thromboembolism).

Table 2: Adverse events profile and safety assessment for 7 days

Adverse events	Control group	Intervention group
Patients with at least one AE; n (%/N patients)	8 (80.0)	6 (54.6)
95% CI	44.4%; 97.5%	23.4%; 83.3%
Patients with at least one serious adverse event (SAE)	5 (50.0)	2 (18.2)
Patients with at least one AE of severe intensity	4 (40.0)	1 (9.1)
Patients with any AEs	-	0 (0.0)
Patients with at least one SAE associated to Gamma globulin administration	-	0 (0.0)
* 80% CI	-	0.0; 0.14
* 95% CI	-	0.0; 0.24
& 95% CI	-	0.0; 0.22
• Probalities of serious AEs associated with the treatment	-	0.08
• Probalities of serious AEs >0.10 associated with the treatment	-	0.28
Number of AEs reported; n (n% of AE)	22 (100.0)	13 (100.0)
AEs associated with treatment	-	0 (0.0)
Serious AEs	14 (63.6)	2 (15.4)
Serious AEs associated with treatment	0 (0.0)	0 (0.0)
AEs with low intensity	4 (18.2)	3 (23,1)
AEs with moderate intensity	9 (40.9)	9 (69,2)
Serious Aes	9 (40.9)	1 (7.7)
Serious AEs associated with treatment	0 (0.0)	0 (0.0)
Types of adverse events with frequency greater than 2 per groups		
Arterial Hypertension	1 (4,50)	4 (30,8)
Hypoxemia	3 (13,60)	1 (7,70)
Acute respiratory failure	3 (13,60)	1 (7,70)
Pulmonary thromboembolism	2 (9,10)	0 (0.0)
Fever	1 (4,50)	2 (15,40)

Legend: 95 % CI. 95% Confidence Interval (exact bilateral); * 80 % CI: 80 % exact one-sided confidence interval limit; * 95 % CI: 95 % exact one-sided confidence interval limit; & 95 % CI: 95% probability interval of maximum verosimilarity

Table 3 shows the frequency of patients with improvements in anti-inflammatory and antiviral parameters, severity parameters, and pulmonary involvement assessed by imaging. In the group that received anti-SARS-CoV-2 immunoglobulin, 72% of patients had negative PCR tests on day 5 of admission. Seven days after treatment, 81.8% had increased PCR Ct values and decreased C-reactive protein levels; in addition, 72.7% showed a decrease in INL, while only 27.3% of the 11 patients showed a decrease in D-dimer.

Table 3: Frequency of patients with improvement in markers of anti-inflammatory and antiviral response, severity criteria, and lung involvement assessed by images at 7 days

Variables	Control group	Intervention group
Improvement in anti-inflammatory and antiviral parameters		
Increased PCR Ct values, n (%)	7 (70.0)	9 (81.8)
95% CI	34.8; 93.3	48.2; 97.7
Decrease in INL, n (%)	3 (30.0)	8 (72.7)
95% CI	6.7; 65.3	39.0; 94.0
Decreased C-reactive protein, n (%)	5 (50.0)	9 (81.8)
95% CI	18.7; 81.3	48.2; 97.7
Decrease in D-dimer, n (%)	3 (30.0)	3 (27.3)
95% CI	6.7; 65.3	6.0; 61.0
Increased PCR Ct values and decrease in INL, C-reactive protein, and D-dimer), n (%)	1 (10.0)	2 (18.2)
95% CI	0.3; 44.5	2.3; 51.8
Moment of RT-PCR negativization		
Day 3, n (%)	3 (30.0)	5 (45.5)
95% CI	6.7; 65.3)	16.8; 76.6
Day 5, n (%)	6 (60.0)	8 (72.7)
95% CI	26.2; 87.8	39.0; 94.0
Day 7 (n (%)	7 (70.0)	8 (72.7)
95% CI	34.8; 93.3	39.0; 94.0
Improvement in severity criteria		
*Oxygen saturation (SpO2) ≥ 93%, n (%)	7 (70.0)	8 (72.7)
95% CI	34.8; 93.3	39.0; 94.0
Improved or remained without the need for oxygen, n (%)	3 (30.0)	9 (81.8)
95% CI	6.7; 65.3	48.2; 97.7
* PaO2/FiO2 ratio ≥ 250 mm Hg, n (%)	5 (50.0)	9 (81.8)
95% CI	18.7; 81.3	48.2; 97.7
* Respiratory Rate ≤ 25, n (%)	7 (70.0)	11(100.0)
95% CI	34.8; 93.3	71.5; 100 **
Improvement of lung involvement through image assessment		
Favorable or stationary response observed on X-ray, n (%)	7 (70.0)	10 (90.9)
95% CI	34.8; 93.3	58.7; 99.8
Favorable response observed on CT, n (%)	1 (10%)	5 (45.5)
95% CI	0.3; 44.5	16.8; 76.6

There was a decrease in the median values of the anti-inflammatory response markers in both groups and this decrease was more accentuated in INL and C-reactive protein in the group that received Gamma globulin. The INL had a Median (p_{25}- p_{75}) change (D_7-D_0) in -1.3 values (-4.5- 0.0) and C-reactive protein; and both had a statistically significant decrease (p=0.017 and p=0.013, respectively).

All parameters indicative of severity remained stable or improved in more than 72% of the patients who received Gamma globulin. An improvement of lung involvement was observed on X-ray, given to the favorable evolution or no worsening in the lesions observed on images of 10/11 patients (95% CI [58.7; 98.7]) and on the CT of 5/11 patients (45.5%, 95% CI [16.7; 76.6]). (Table 3). Only 2/11 patients worsened (18.2%; 95% CI [2.3; 51.8]). No patient required mechanical ventilation.

In the control group, response rates were lower than 70% for all markers; lung involvement improved in 70% of patients according to the X-ray criteria and in 1/10 patients according to CT. The percentage of subjects with improvement in severity criteria was 70% or lower for each parameter (Table 3).

The median and interquartile range of hospital stay (days) were 11(9 -12) for the intervention group and 15.5 (11.5 - 18.5) for the control group. The median and interquartile range of the time (days) in the Intensive Care Unit (ICU) were 7.5 (7-8) and 12.5 (8 - 22), in the intervention and control groups, respectively.

DISCUSSION

There is no specific treatment for COVID-19. Current measures are basically supportive, so the need to ensure supportive care is essential in order to minimize complications.[15,16] In theory, the successful treatment of this infection should neutralize the virus, induce an antibody-dependent cytotoxicity response, and remove the circulating viral agents.[17]

The anti- SARS-CoV-2 Gamma globulin is a new product of Cuban biotechnology that presents high titers of IgG antibodies which are similar to others described worldwide.[6,7] Its administration neutralizes the virus and promotes the patient´s recovery by modifying the immune system.[6,18]

Immunotherapy using IgG combined with antiviral drugs is useful for treating and preventing SARS-CoV-2 infection.[18]

The anti- Sars-CoV-2 Gamma globulin associated with the treatment of seriously ill patients evidenced safety in this study. None of the patients experienced adverse events causally related to the treatment, an aspect which is consistent with other trials in which intravenous immunoglobulins were also used.[19] In a review article, Oreiro[17] pointed out that purified immunoglobulin preparations are a safer option that presents greater activity than convalescent plasma. As they are produced by combining the plasma obtained from several patients, they are capable of increasing polyvalency of antibodies against the virus, thus becoming a better patients' treatment choice at advanced stages of infection with a more severe clinical presentation. This aspect is consistent with the study, since the intervention scenario involved seriously ill patients.

The authors also add that the analyses carried out so far indicate that this therapy, which is also based on passive immunization with antibodies, is very promising in a context where there is an absence of other specific therapies.

Some differences in relation to dosage have been presented in different studies. According to Focosi *et al*.,[6] the dosage ranges from 0.1 to 0.4 grams per kilograms of body weight, and it is repeated between 1 and 3 days. However, a study that compiles information on 16 clinical trials that evaluated the use of anti-SARS-CoV-2 Gamma Globulin, allowed to determine that the dosing range and dosage intervals are variable (from 0,1g to 4g per kg of body weight), as a single or fractionated dose, depending on the severity of the clinical picture and the concentrations of the finished product, an aspect coinciding with this trial in which a single dose of 0.15 g per kg of body weight was evaluated.

There are few reports in relation to serious adverse events with the use of IVIG to treat COVID-19. (5,6,20,21) Ali S. *et al*.[20] consider that the treatment with IVIG on the management of COVID-19 patients is safe, with no immediate or serious adverse events related to drug use. Authors such as Liu J *et al*.[22] suggest the safety and efficacy of a single dose, an aspect which is consistent with this study, since the reported adverse events were not related to the administration of the product but to the progression of the disease.

The decrease in Ct values, or minimum amplification cycles for virus detection by PCR from the time of diagnosis and in the days following administration is an indicator of the antiviral effect of the drug.

The evaluation of the antiviral and anti-inflammatory response was determined by the behavior of the PCR Ct values and the D-dimer. Shaukat *et al*.[23] also evaluated the neutrophil-to-lymphocyte ratio and C-reactive protein, detecting a decrease in these inflammatory parameters after treatment administration.

Another study that evaluated the effectiveness of anti- Sars-CoV-2 immunoglobulins in seriously ill COVID-19 patients revealed a decrease in inflammatory parameters such as C-reactive protein as well as a favorable antiviral response with negative PCR results obtained on the fifth day of treatment.[24] This study demonstrated that Ct values increased on the third day, with negativization of PCR on day 5 of evaluation. In a research article, Cadiz[8] raises the importance of treatment with intravenous immunoglobulins in infectious diseases due to its antiviral properties.[25] The treatment with IVIG, administered at the early stages of the disease (within 72 hours after the onset of symptoms) and high titers (>1:160) of anti-SARS-CoV-2 neutralizing antibodies (nAbs), is associated with clinical benefit, since it decreases disease progression, hospitalization, and mortality.[20] González[26] states that this treatment is effective by neutralizing SARS-CoV-2, immunomodulating cytokines, and preventing bacterial infection due to the presence of polyclonal antibodies against other opportunistic pathogens.

The downregulation of B and T lymphocyte cell functions by the use of IVIG prevents organic failure and subsequent mortality.[27] None of the 11 patients included and treated in this study required mechanical ventilation, the clinical data did not evidence any critical condition during their hospital stay,[15] and only one patient died from complications of the disease. These results could be associated with the use of the product.

The average time of hospital stay was from 3.0 to 1.0 days. In a study involving similar design, Payam[21] reported an average time of hospital stay of about 3.84 and 3.35 days from admission to the beginning of treatment, as well as a decrease in severity parameters.

González[26] indicates that the treatment is effective at initial stages of the disease. The evidence of greater numbers of patients' discharges from hospital and a lower frequency of intubation was significant, which is in accordance with this study because none of the patients included were receiving mechanical ventilation (at the time of selection).

A multicenter study that included three cities in China demonstrated the benefit of the use of intravenous immunoglobulins in seriously ill COVID-19 patients for less than 7 days to decrease oxygen therapy and increase survival. [28] This evidence coincided with the results obtained in this study as all patients were treated in a period of less than 10 days, decreasing the need for oxygen therapy, the respiratory rate and the PaO2/FiO2 ratio by more than a 70%.

Sachin Gaután[29] evaluated the evolution of respiratory rate, the partial saturation of oxygen, and the presence of inflammatory lesions after the administration of IVIGs for 9 days. In 96% of patients, the respiratory rate and oxygen saturation of patients improved after the sixth day of treatment and the radiological inflammatory lesions of all the patients showed a reduction when comparing the first with the ninth day of treatment. In this research study, the improvement of lung lesions was detected after the 7th day of treatment in the group under treatment.

The strength of the randomized design to obtain similar concurrent control of its basal characteristics was not obtained; therefore, the analysis of the results with direct assessment of the concurrent control loses its value. However, the study allowed us to estimate the magnitude of the changes produced by anti- SARS-CoV-2 hyperimmune gamma globulin within the parameters of antiviral, anti-inflammatory and clinical response in a population of seriously ill COVID-19 patients at the 7th day of treatment. These are the first results obtained from the clinical evaluation of this product, which serve as a basis for further studies related to its clinical development.

CONCLUSIONS

The clinical, anti-inflammatory and antiviral response obtained in patients treated with anti- Sars-CoV-2 gamma globulin was favorable at the 7th day of treatment, demonstrating the safety of the product.

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Conflict of interests

The authors have no conflicts of interests to declare.

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